DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE

OCRIPLASMIN (JETREA™) BRIEFING DOCUMENT

BLA 125422

Advisory Committee Meeting

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ThromboGenics Inc.

101 Wood Avenue South
Iselin, New Jersey 08830

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EXECUTIVE OVERVIEW

Introduction

Symptomatic vitreomacular adhesion (VMA) can be a progressive, sight-threatening condition that results from incomplete separation of the vitreous from the macula. The only available intervention is vitrectomy, a major surgical procedure that is often reserved until symptoms become severe and intervention unavoidable. No pharmacologic treatments are currently available for these patients.

ThromboGenics has developed ocriplasmin (JETREA™) intravitreal injection to advance the treatment of patients with symptomatic VMA. Ocriplasmin is designed to liquefy the vitreous and cleave the components of VMA to resolve the underlying condition. The 2 randomized, Phase 3, placebo-controlled studies, TG-MV-006 and TG-MV-007, enrolled symptomatic VMA patients, characterized as vitreomacular traction (VMT) with or without a full thickness macular hole (FTMH). Each study achieved its primary endpoint, with statistically significantly higher rates of resolution of VMA at Day 28 in patients treated with a single injection of 125 µg ocriplasmin, versus placebo. These studies also demonstrated an acceptable safety profile in 465 patients exposed to ocriplasmin.

As the first pharmacologic treatment for symptomatic VMA, ocriplasmin offers a new approach to resolving VMA. A pharmacologic treatment has the potential to alter the treatment paradigm by allowing earlier intervention with the possibility of limiting progression and thereby improving outcomes.

The proposed indication for ocriplasmin is the treatment of symptomatic VMA including macular hole. The recommended dose is 125 µg to be administered by a single intravitreal injection in a volume of 100 µL.

The scientific and medical rationale, clinical evidence, and benefit-risk profile of ocriplasmin are summarized in this overview, followed by a more detailed presentation of the nonclinical and clinical findings.

Therapeutic Rationale

Symptomatic VMA can be a progressive, sight-threatening condition that results from incomplete separation of the vitreous from the macula (Section 1). Under normal physiologic conditions, the vitreous maintains a gel-like consistency and adheres completely to the entire surface of the retina. The consistency of the vitreous and the adhesion are both maintained by a matrix of proteins including collagen, laminin, and fibronectin, among others. As part of the normal aging process, the vitreous undergoes a gradual breakdown of this protein structure, resulting in a progressive liquefaction and subsequent separation of the vitreous from the retina, a process referred to as posterior vitreous detachment (PVD) (Figures 1 and 2) (Larsson 1985, Sebag 2005, Schneider 2011).

Figure 1. Posterior Vitreous Detachment

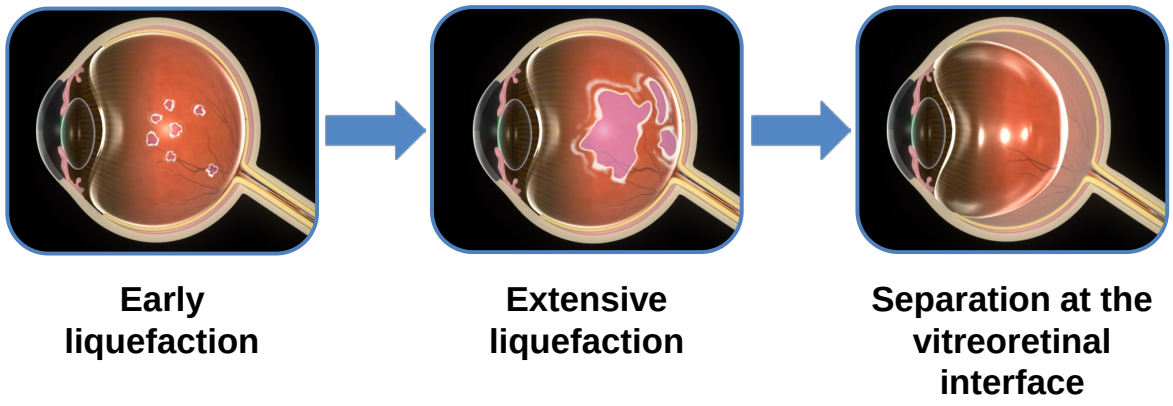
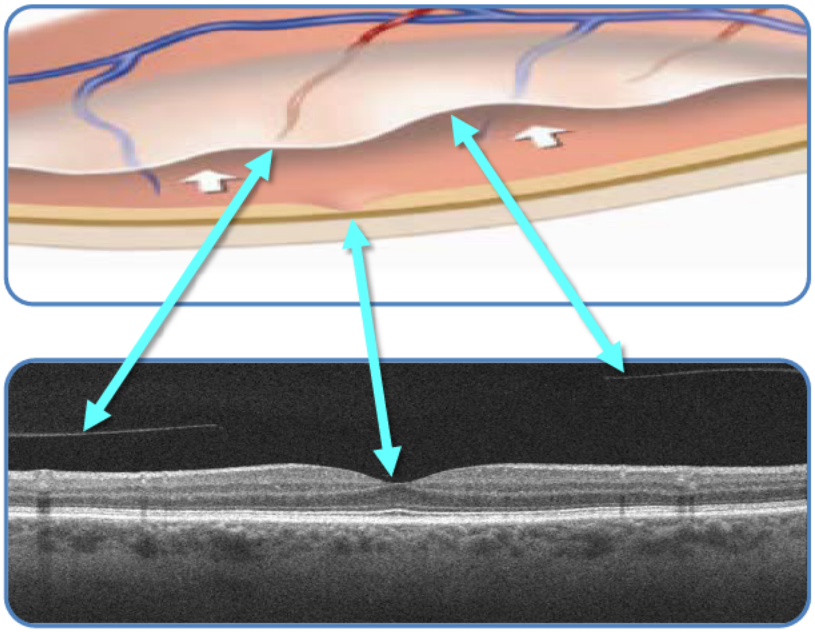


Figure 2. Normal Vitreomacular Separation

Right and left arrows show areas of complete separation of the vitreous. Middle arrow shows normal foveal depression.



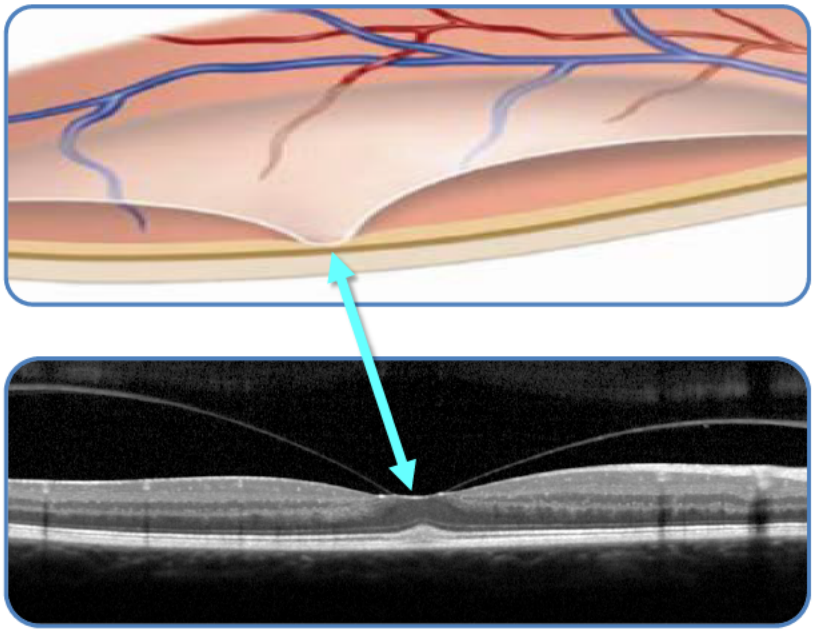
Optical coherence tomography image of the retina and vitreomacular interface.

Top panel adapted with permission from *Clinical Ophthalmology*, volume 5: Takezawa M, Toyoda F, Kambara C, et al; Clarifying the mechanism of idiopathic macular hole development in fellow eyes using spectral-domain optical coherence tomography, pages 101-108, ©2011, with permission from Dove Medical Press Ltd.

Usually, the PVD process proceeds without incident. Occasionally, however, the adhesion between the vitreous and the retina does not weaken sufficiently to allow for complete separation. Typically, the adhesion remains at sites where the bonds between the vitreous and the retina are strongest, including the macula (Schneider 2011). The macula is the primary area of the retina responsible for central vision. Adhesion at the macula is known as VMA (Figure 3).

Figure 3. Vitreomacular Adhesion

Arrow shows point of adhesion at the macula of a patient with VMA.

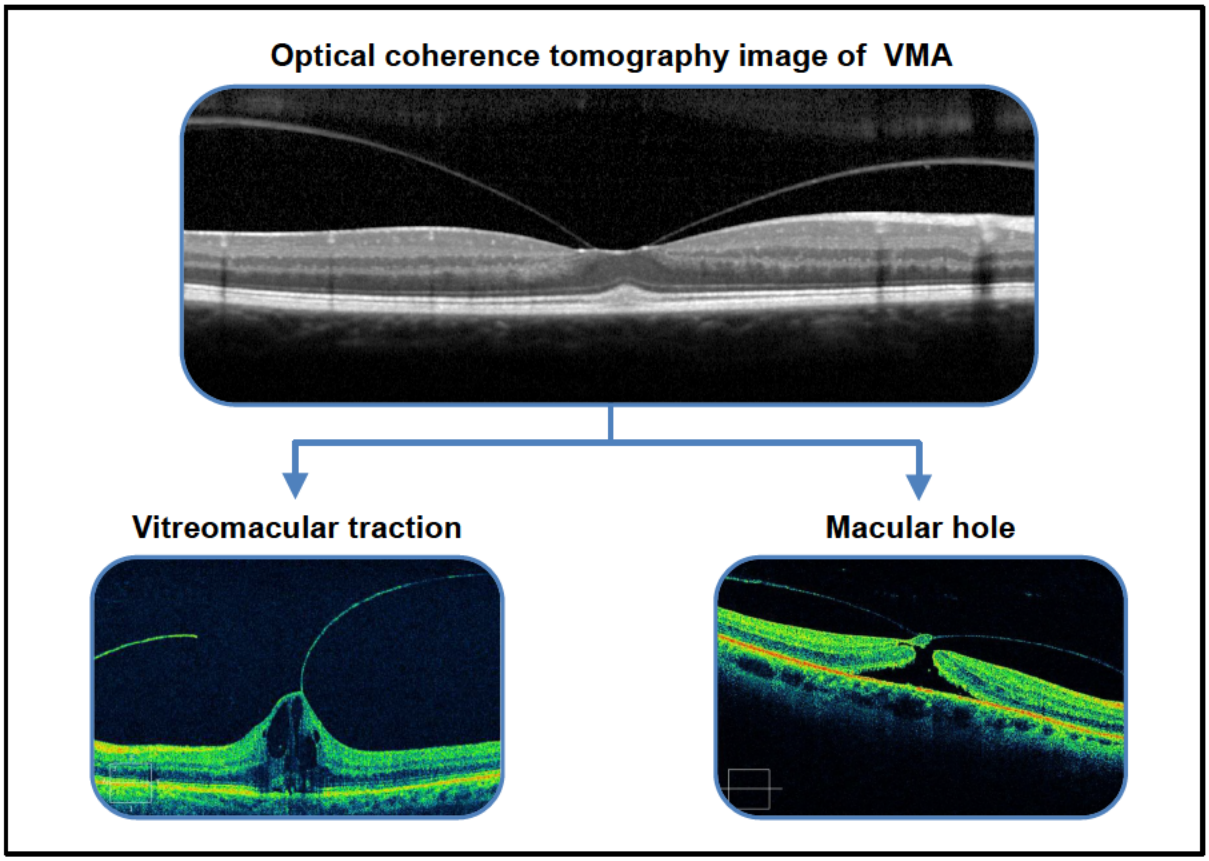


Optical coherence tomography image of the retina and vitreomacular interface.

Abbreviation: VMA, vitreomacular adhesion.
Top panel adapted with permission from *Clinical Ophthalmology*, volume 5: Takezawa M, Toyoda F, Kambara C, et al; Clarifying the mechanism of idiopathic macular hole development in fellow eyes using spectral-domain optical coherence tomography, pages 101-108, ©2011, with permission from Dove Medical Press Ltd.

Early in the disease process, VMA begins to exert tractional force at the retinal surface, which compromises the structural and functional integrity of the macula (Sebag 2004, Schneider 2011). The most common manifestations of this phenomenon are VMT and macular hole (Figure 4).

Figure 4. Symptomatic VMA



Abbreviation: VMA, vitreomacular adhesion.

Patients with these conditions can present with a range of symptoms, which may include (but are not limited to) diminished visual acuity, distorted vision (metamorphopsia), and central visual field defect (blind spot). These symptoms, many of which are subjective in nature and unquantifiable, can greatly affect a patient's visual function and ability to perform normal daily activities, including reading, driving, watching television, etc.

Epidemiologic data are limited; thus, the precise incidence of symptomatic VMA has not been established. Symptomatic VMA represents a subset of the total population of patients with VMA, since most patients are asymptomatic. Use of optical coherence tomography (OCT), the established gold standard in diagnosing and managing diseases of the retina and vitreoretinal interface, is expected to lead to an increase in the number of patients diagnosed with VMA. A recent screening study using OCT found VMA present in 22% of 568 eyes, in the absence of

frank symptomatology (Thomas 2012). Schwab and colleagues reported that 19% of 335 consecutive eyes had adhesions at the macula (Schwab 2012).

The limited natural history data indicate that only 10% of patients with symptomatic VMA resolve spontaneously. In most patients, the disease continues to progress (Hikichi 1995, Kim 1996), leading to loss of vision which may be irreversible as a result of prolonged anatomic damage (Sonmez 2008). Most patients face an uncertain future of progressive vision loss and worsening symptoms.

The current treatment paradigm for symptomatic VMA is to observe patients ("watchful waiting") until visual symptoms deteriorate to the point that vitrectomy, the only current intervention, is justified. This surgical procedure entails removal of the vitreous gel of the eye and may include the peeling of retinal membranes. While highly effective in achieving separation of the vitreous from the retina, vitrectomy is not performed earlier in the disease process due to known intraoperative and post-operative risks, including retinal detachment, hemorrhage, intraocular infection, cataract formation, and others (Guillaubey 2007, Ramkissoon 2010, Rizzo 2010, Banker 1997, Chen 1998, Park 1995, Thompson 1996, Recchia 2010, Freeman 1997, Cheng 2001). In phakic patients, cataract formation will almost always necessitate a second operation within 2 years to replace the opacified lens (Holekamp 2005).

The recovery period after vitrectomy can be extensive. The patient may need to remain immobilized in a "head-down" position for 7 to 14 days and be dependent on caregivers. For these reasons, physicians usually monitor their patients with a watchful-waiting approach, and reserve vitrectomy until symptoms become severe.

The duration of watchful waiting is variable, as the decision to perform vitrectomy is dependent on the patient's visual needs for daily life and the rate of disease progression. During this period, patients are closely monitored with clinical examinations and OCT scans, and physicians and patients repeatedly discuss the pros and cons of intervening in view of how symptoms are affecting the patient's personal and/or professional lives.

Among patients who undergo vitrectomy, those with less vision loss and a shorter duration of symptoms before surgery tend to have better improvement in visual acuity following surgery (Melberg 1995, Sonmez 2008). This suggests that earlier treatment might achieve better

outcomes. Thus, there is a pressing need for a new, earlier, and less invasive treatment option in patients with symptomatic VMA.

Ocriplasmin is designed to resolve the underlying condition with minimal post-procedure burden on patients and caregivers. Ocriplasmin also offers an earlier treatment option, with the potential to reduce disease progression and complications that increase during the period of watchful waiting.

A single intravitreal injection performed in the ophthalmologist's office can result in resolution of VMA with a low risk of major complications and the possibility of improved outcomes. As the first pharmacotherapy to offer safe and effective treatment of symptomatic VMA, ocriplasmin marks an important advance in the treatment of this disease.

Mechanism of Action

Ocriplasmin is a recombinant truncated form of the human serine protease plasmin (molecular weight, 27.2 kDa) with retained enzymatic activity. The drug's enzymatic properties target the architectural components of the vitreous and the adhesion at the vitreoretinal interface, both of which are implicated in the pathogenesis of symptomatic VMA. Ocriplasmin exerts proteolytic effects on collagen, fibronectin, and laminin to produce vitreous liquefaction and its detachment from the macula (Gandorfer 2004, Sebag 2012).

In multiple preclinical models, intravitreal injection of ocriplasmin consistently and rapidly (within 30 minutes) induced complete vitreous detachment. These experimental results confirmed its potential viability as a pharmacologic treatment of symptomatic VMA.

In clinical pharmacokinetic studies, ocriplasmin was undetectable in the eye within 7 days after a single intravitreal injection. Ocriplasmin administered intravitreally does not result in detectable levels in the systemic circulation. In studies assessing systemic exposure after intravenous administration in humans, ocriplasmin was inactivated quickly (within seconds) by α_2-antiplasmin. The inactive ocriplasmin/α_2-antiplasmin complex is then cleared from the circulation with a half-life of several hours.

Clinical Program

Based on the mechanism of action and preclinical findings with ocriplasmin, ThromboGenics, in collaboration with retina specialists, designed a comprehensive clinical program to assess intravitreal injection of ocriplasmin for the treatment of symptomatic VMA including macular hole. The Phase 2 program included 4 dose-ranging studies that identified an efficacious therapeutic ocriplasmin dose of 125 µg by single intravitreal injection. The ensuing Phase 3 MIVI-TRUST (Microplasmin[1] for IntraVitreous Injection-Traction Release without Surgical Treatment) program comprised 2 randomized, placebo-controlled clinical studies, TG-MV-006 and TG-MV-007, which had identical study designs, except for geographic location of the studies (the United States [US] for TG-MV-006, and the US and Europe for TG-MV-007), and randomization allocation ratios to ocriplasmin versus placebo (2:1 in TG-MV-006, and 3:1 in TG-MV-007) (Section 7).

Efficacy

In the Phase 3, randomized, placebo-controlled TG-MV-006 and TG-MV-007 studies, a total of 652 patients (652 eyes) were randomly assigned to receive a single 100 µL intravitreal injection of ocriplasmin 125 µg (n = 464) or vehicle control as placebo (n = 188) in a double-masked fashion. The placebo consisted of vehicle that was identical to the ocriplasmin injection without the active drug. Vehicle was selected as the placebo control, instead of sham, to ensure masking and that any observed treatment effect in the ocriplasmin group could confidently be ascribed to the drug product.

Patients were eligible for the study if they had VMA on OCT, specifically focal VMA (defined as an adhesion within a 6-mm field of the macula on OCT and surrounded by an elevation of the posterior vitreous cortex); symptoms considered by the investigator to be due to VMA (eg, decreased visual acuity, metamorphopsia, and/or other visual complaints); and a best corrected visual acuity (BCVA) of 20/25 or worse. While the inclusion criteria allowed for this level of visual acuity, the mean baseline visual acuity of patients enrolled in both the ocriplasmin and placebo arms of both studies was 20/50. Other visual symptoms (eg, metamorphopsia) were not

[1] The term microplasmin was routinely used early in the clinical development program before a switch was made to the generic name (ocriplasmin).

followed as part of the Phase 3 studies, due to the lack of validated tools to objectively quantify them. Patients with macular holes measuring >400 µm in diameter were study entry exclusions, as these macular holes are significantly harder to close, even with surgical intervention, compared with macular holes ≤400 µm in diameter.

After receiving the single intravitreal injection of ocriplasmin or placebo, patients were followed for 6 months. The primary endpoint was OCT-confirmed resolution of VMA at Day 28, as determined by a masked central reading center (CRC). Resolution of VMA is considered the most clinically relevant objective endpoint for assessment of treatment effect because these anatomic changes precede functional changes and are universally used to guide treatment decisions. The alpha-protected secondary endpoint was induction of total PVD at Day 28, as determined by masked investigator using B-scan ultrasonography (Sections 7.4.1 and 7.4.2).

Other secondary endpoints are supportive and provide broader evidence of treatment benefit. These include the proportion of patients with closure of macular hole without the need for vitrectomy, proportion of patients not requiring vitrectomy, improvements of ≥2 and ≥3 lines in BCVA without the need for vitrectomy, improvement in BCVA, and improvement in the National Eye Institute (NEI) 25-Item Visual Functioning Questionnaire (VFQ-25). Results of these endpoints are described with nominal 95% confidence intervals (CIs) and nominal *P* values without any statement of statistical significance.

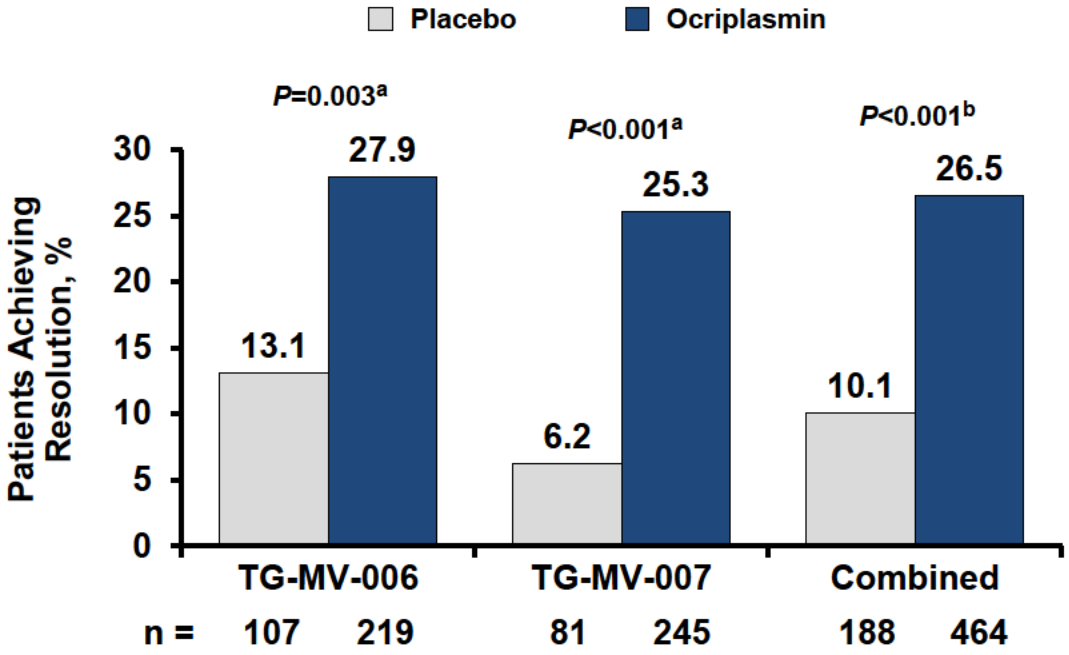
Baseline Demographics

At baseline, demographic and ocular characteristics were generally comparable among the 652 randomized patients. The majority were female (65.8%), most were white (92.3%), and the mean age was 72 years. All patients had symptomatic VMA (defined above) at baseline; all of these patients were characterized as having VMT with 23.5% having FTMH (Section 8.2.2).

Results for the Primary Endpoint − VMA Resolution

In each randomized, placebo-controlled study, ocriplasmin demonstrated a statistically significant treatment effect for the resolution of VMA at Day 28. These results were confirmed in the combined analysis (Figure 5). The majority of ocriplasmin-treated patients achieved the primary efficacy endpoint by the first post-injection visit (Day 7). This difference was maintained through the end of the 6-month follow-up period for both studies.

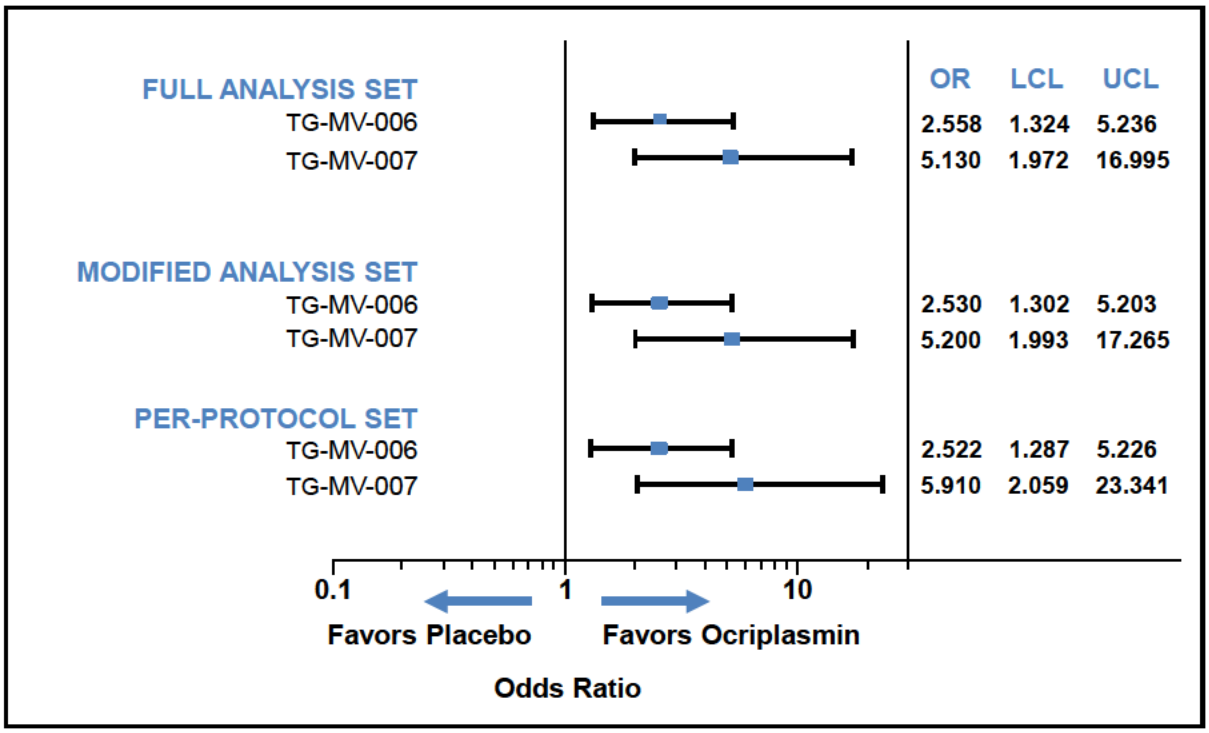
Figure 5. Primary Efficacy Endpoint: Proportion of Patients with VMA Resolution at Day 28 (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set)



Abbreviation: VMA, vitreomacular adhesion.
[a]Fisher's exact test; [b]Cochran-Mantel-Haenszel test, stratified by study.
Note: Full Analysis Set included all randomized patients who received treatment; data analyzed according to randomized patient-treatment group regardless of treatment actually received.
Data on file, ThromboGenics.

Sensitivity analyses confirmed the consistent and significant treatment effect of ocriplasmin for achievement of the primary endpoint (Figure 6).

Figure 6. Odds Ratios (with 95% CIs) of the Comparison of Ocriplasmin versus Placebo for VMA Resolution at Day 28 (All Analysis Sets)



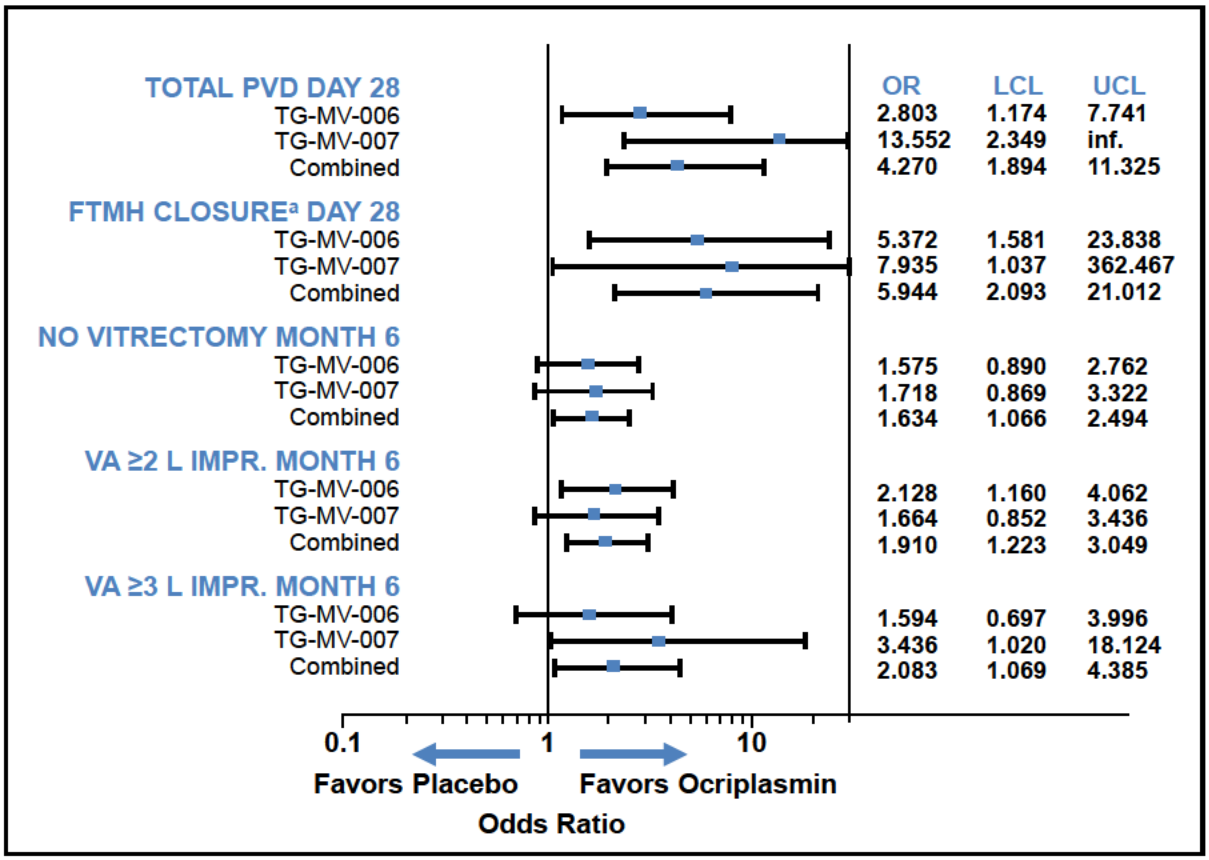
Abbreviations: CI, confidence interval; LCL, lower confidence limit; OR, odds ratio; UCL, upper confidence limit; VMA, vitreomacular adhesion.
Note: Full Analysis Set included all randomized patients who received treatment; Modified Full Analysis Set excluded patients without VMA at baseline according to central reading center evaluation of optical coherence tomography image; Per-Protocol Set included the Full Analysis Set but excluded patients with serious protocol deviation (see Section 7.4.3 and Table 10).
Data on file, ThromboGenics.

In the multiple regression model adjusted for baseline covariates, significance of the treatment effect was maintained for the proportion of patients who achieved VMA resolution at Day 28. Consistent with the multiple regression analysis, the subgroup analyses showed treatment differences in favor of ocriplasmin across subgroups defined by age, epiretinal membrane (ERM), macular hole, and lens status (Section 8.2.3.2).

Results for the Secondary Endpoints

There was a clear treatment benefit of ocriplasmin relative to placebo for each Phase 3 study and the combined analysis in terms of all categorical secondary endpoints (Figure 7).

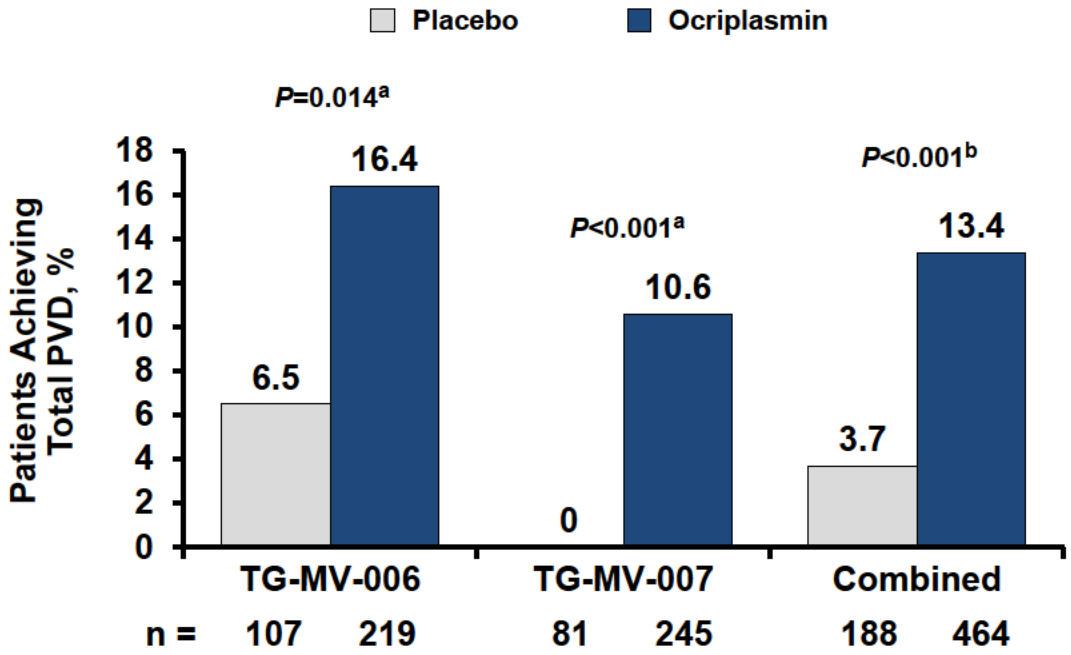
Figure 7. Odds Ratios (with 95% CIs) of the Comparison of Ocriplasmin versus Placebo for the Secondary Endpoints (Full Analysis Set)



Abbreviations: CI, confidence interval; FTMH, full thickness macular hole; IMPR., improvement; L, line; LCL, lower confidence limit; OR, odds ratio; PVD, posterior vitreous detachment; UCL, upper confidence limit; VA, visual acuity.
[a]Without vitrectomy.
Data on file, ThromboGenics.

In both Phase 3 studies and the combined analysis, significantly more patients treated with ocriplasmin than placebo showed total PVD at Day 28 (Figure 8) (Section 8.2.4.1). Thus, the investigator-determined B-scan ultrasonography results are supportive of the centrally read OCT results for VMA resolution.

Figure 8. Proportion of Patients with Total PVD at Day 28 (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set)



Abbreviation: PVD, posterior vitreous detachment.
[a]Fisher's exact test; [b]Cochran-Mantel-Haenszel test, stratified by study.
Data on file, ThromboGenics.

In addition, mean improvements from baseline in BCVA, irrespective of vitrectomy, favored ocriplasmin, with a maximum improvement of 3.6 letters in the ocriplasmin group at end of the study.

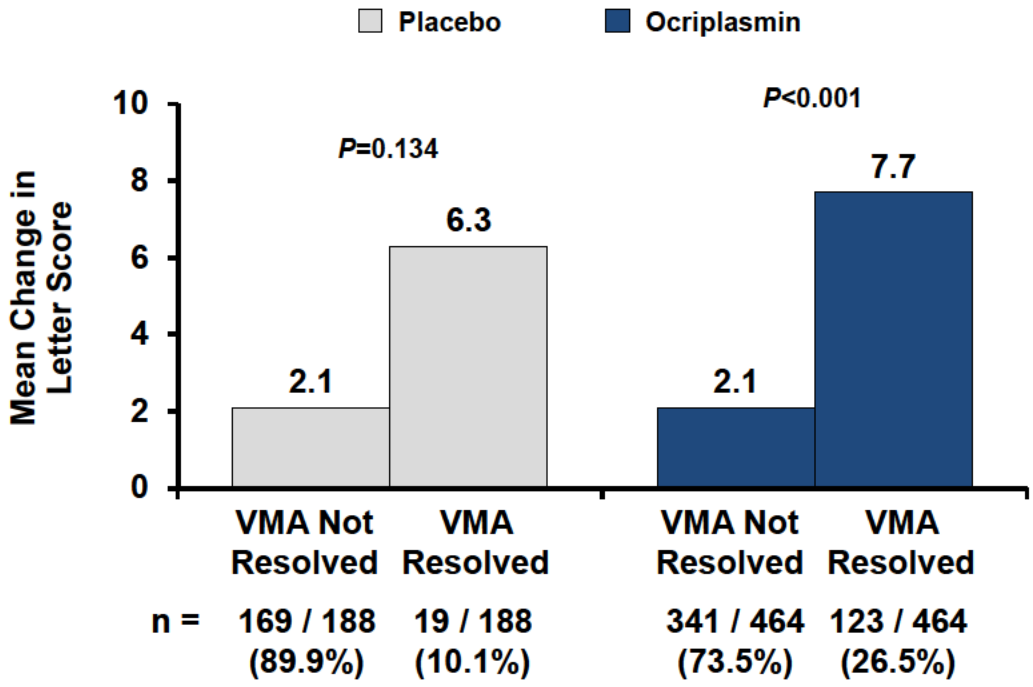
The VFQ-25 results also provide patient-reported evidence of the benefit of ocriplasmin. In the combined analysis, the improvement in the general vision subscale score was 6.1 for ocriplasmin and 2.1 for placebo, and in the composite score was 3.4 and 0.7, respectively, at Month 6 (Section 8.2.4.6).

Association between Anatomic and Functional Improvements

Resolution of VMA and closure of FTMH are the goals of vitrectomy in these conditions. Vitrectomy has established the association between resolution of anatomic pathology and functional improvements, including BCVA and VFQ-25 scores (Ezra 2004, Hirneiss 2007, Larsson 2004, Okamoto 2010, Witkin 2010). In the TG-MV-006 and TG-MV-007 studies, such associations were observed between anatomic resolution and functional improvements (Section

8.2.5). In ocriplasmin-treated patients who achieved VMA resolution at Day 28 (n=123), 45% had a ≥2-line improvement and 20% had a ≥3-line improvement in BCVA at Month 6 (baseline BCVA was 61.7 letters, 20/63). Improvement in mean BCVA in these patients was 7.7 letters compared with 2.1 letters in ocriplasmin-treated patients who did not achieve VMA resolution (Figure 9).

Figure 9. Improvement in Mean BCVA at Month 6 by Resolution of VMA at Day 28 (Combined Analysis: Full Analysis Set)



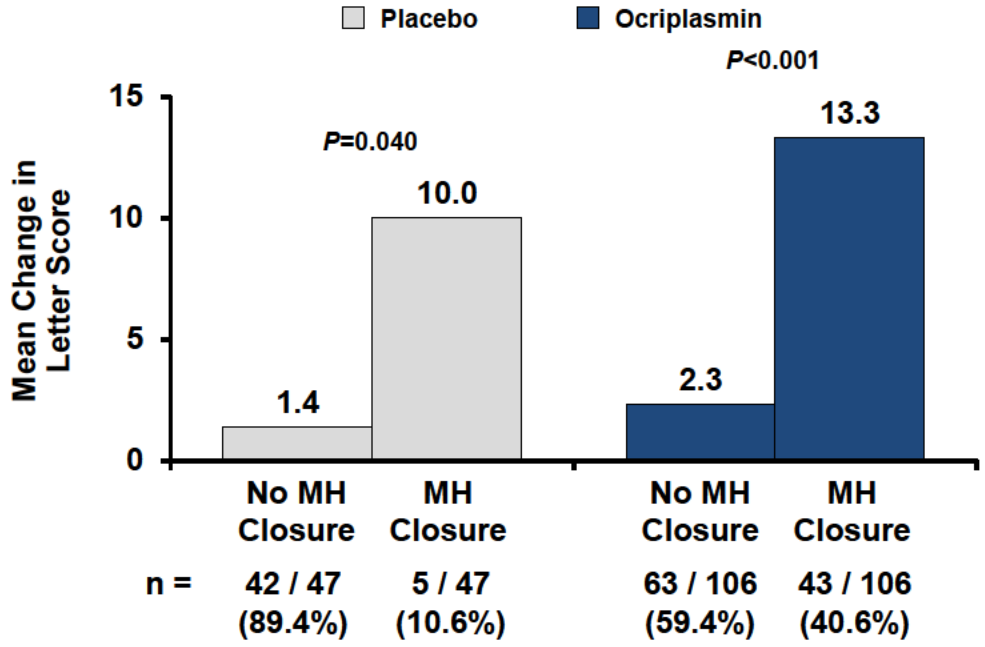
Abbreviation: BCVA, best corrected visual acuity; VMA, vitreomacular adhesion.
For individual studies, treatment groups are compared with respect to the change from baseline using analysis of variance model with factors for treatment and baseline visual acuity category (<65, 65-75, >75); for combined analysis, the model also includes a factor for study.
Data on file, ThromboGenics.

In ocriplasmin-treated patients who achieved non-surgical FTMH closure at Day 28 (n = 43/106), BCVA improved by ≥2 lines in 72.1% and by a ≥3 lines in 48.8% of patients at Month 6 (baseline BCVA was 57.7 letters, 20/80). Mean improvement from baseline in BCVA was greater at Month 6 among ocriplasmin-treated patients who achieved non-surgical macular hole closure (13.3 letters) compared with those who did not (2.3 letters) (Section 8.2.5.2) (Figure 10). Similar changes were seen in placebo-treated patients who achieved VMA resolution and

FTMH closure at Day 28, compared with placebo-treated patients who did not achieve these outcomes.

VMA resolution and macular hole closure were also associated with improvements in NEI VFQ-25 scores (Section 8.2.5.3). At Month 6, the mean improvements from baseline in VFQ-25 general vision and composite scores for ocriplasmin-treated patients who achieved VMA resolution at Day 28 were 8.4 and 5.7, respectively. The corresponding improvements in mean scores at Month 6 in patients who achieved non-surgical macular hole closure were 16.0 and 9.0, respectively.

Figure 10. Improvement in Mean BCVA at Month 6 by Macular Hole Closure at Day 28 (Combined Analysis: Full Analysis Set)



Abbreviation: BCVA, best corrected visual acuity; MH, macular hole.
For individual studies, treatment groups are compared with respect to the change from baseline using analysis of variance model with factors for treatment and baseline visual acuity category (<65, 65-75, >75); for combined analysis, the model also includes a factor for study.
Data on file, ThromboGenics.

In summary, results of 2 Phase 3, randomized, placebo-controlled studies demonstrated the efficacy of ocriplasmin for the treatment of symptomatic VMA including macular hole. Ocriplasmin treatment resulted in significantly higher rates of VMA resolution at Day 28 as confirmed by OCT, compared with placebo. Induction of a total PVD, the alpha-protected

secondary endpoint, is supportive of VMA resolution for the assessment of treatment affect. Furthermore, 40.6% of ocriplasmin-treated patients with a FTMH at baseline achieved non-surgical macular hole closure at Day 28. The onset of ocriplasmin's effect was rapid and was sustained for the duration of the studies. Subgroup analyses confirmed the efficacy of ocriplasmin for the primary endpoint across all subgroups defined by various demographic and ocular characteristics at baseline. Results of other secondary endpoints provided additional evidence of the efficacy of ocriplasmin. Successful VMA resolution and closure of FTMH were strongly associated with functional improvement, as determined by changes in BCVA and VFQ-25 scores. Overall, the results were robust and consistent across endpoints, analyses, subgroups, and studies. The results from TG-MV-006 and TG-MV-007 demonstrate that treatment with ocriplasmin is effective in resolving the underlying pathology of VMA, which results in functional improvements.

Safety

The safety of ocriplasmin has been demonstrated in a comprehensive development program that included 6 to 12 months of follow-up after administration of the drug (Section 9). A total of 741 patients from 7 completed studies received ocriplasmin intravitreal injection; of these, 582 patients received the recommended dose of 125 µg, and 465 received the recommended dose in the Phase 3, randomized, placebo-controlled studies. All except 12 patients received a single intravitreal dose: 3 patients received ocriplasmin in the fellow eye (these patients participated in more than 1 study), and 9 patients received 2 (n = 2) or 3 (n = 7) doses in the same eye at monthly intervals (in studies that allowed additional doses in nonresponders). Subsequent to the database cut-off date of the Biologic License Application (BLA) submission, an additional 235 patients had received ocriplasmin in ongoing clinical studies.

Ocriplasmin is recommended to be administered as a single intravitreal injection. Systemic exposure following intravitreal injection is expected to be negligible, as studies of intravenous administration in humans indicate that ocriplasmin was inactivated within seconds by α_2-antiplasmin. The 6- to 12-month follow-up after a single intravitreal injection demonstrates that ocriplasmin has an acceptable safety profile.

The focus of the safety data is primarily on patients treated in the 2 Phase 3, randomized,

placebo-controlled studies. Data for events of special interest (acute vision decrease, dyschromatopsia, electroretinogram [ERG] changes, and lens findings) include patients in all completed and ongoing studies as of the safety data cut-off date of May 31, 2012.

Patient Disposition, Discontinuation, and Death

Patient disposition was similar between treatment groups, with more than 90% of patients completing the studies. No meaningful difference in the rates of discontinuation for adverse events (AEs) or other reasons was reported. Deaths occurred in 6 of 741 patients treated with ocriplasmin and 2 of 247 control patients (incidence of 0.8% in both groups); no deaths were considered drug-related (Sections 9.3 and 9.4).

Ocular Adverse Events Associated with Ocriplasmin Administration

Ocriplasmin was generally well tolerated. All AEs that were considered suspected adverse drug reactions, ie, there was a reasonable possibility that these events were treatment-related, were ocular, consistent with the route of administration, or mechanism of action. A higher proportion of patients treated with ocriplasmin compared with placebo had at least 1 event in the study eye. The majority were considered mild or moderate in intensity. The rate of AEs considered severe by the investigator was lower in the ocriplasmin group compared with placebo. The rate of Serious AEs in the study eye was also lower in the ocriplasmin group.

Among the AEs that did occur with a higher frequency in the ocriplasmin group, most were consistent with the intended drug effect of pharmacologic vitreolysis (ie, events associated with induction of PVD, such as vitreous floaters or photopsia) or were related to the injection procedure, such as intraocular inflammation and irritation. In addition, the difference in event rates between the ocriplasmin and placebo groups was driven by AEs that occurred within 7 days after injection. No relevant difference was seen between treatment groups for AEs with onset from Day 8 to the end of study, as would be expected with a single-dose therapy with rapid inactivation (Section 9.4.2).

Procedural Risks

No cases of intraocular infection were reported in patients who received ocriplasmin or control in completed and ongoing studies. The overall incidence of intraocular inflammation was higher in

patients treated with ocriplasmin than with placebo. Most events were considered mild and none were Serious (Section 9.4.4.3). No clinically relevant changes from baseline in intraocular pressure (IOP) were observed in either treatment group in TG-MV-006 or TG-MV-007. There were 3 cases of transient increases in IOP that were reported as Serious AEs, in on-going masked studies. All cases were considered probably-related to the injection procedure and resolved without sequelae. Acute increases in IOP are known risks of intravitreal injection (Aiello 2004, Jager 2004, Kuppermann 2005).

The rate of cataract reported as AEs among phakic patients was lower with ocriplasmin than with placebo, and fewer ocriplasmin-treated patients developed retinal breaks (retinal tears and retinal detachments), consistent with the lower rate of vitrectomy in this group (Sections 9.4.5 and 9.4.6).

Acute Vision Decrease

The most notable safety findings, experienced by 9 of 976 ocriplasmin-treated patients, were temporary, post-injection, Serious and/or severe AEs related to acute vision decrease. These patients had substantial initial decreases in vision within 24 hours of injection. The reduced vision returned to pretreatment or better levels, with the exception of 1 patient whose ongoing decreased vision was not considered by the investigator to be related to ocriplasmin, but rather to the concurrent retinal disease (macula-off retinal detachment and exudative age-related macular degeneration). The median time to full recovery of visual acuity was 2 weeks; the longest was 1 year in a patient who required cataract surgery which was unrelated to study treatment (Section 9.5.1.).

Changes in Color Vision/Electroretinogram

Dyschromatopsia was reported in 17 patients treated with ocriplasmin (described as yellow-tinted vision). Thirteen of 17 cases were reported from a single center that participated in 2 uncontrolled open-label clinical studies. Symptoms were rated as not Serious and mild in all but 1 case and the dyschromatopsia resolved in 13 patients (Section 9.5.1.2).

ERG changes were reported in 11 of 141 ocriplasmin-treated patients who had ERG evaluations (described as a- and b-wave amplitude decreases occurring in the first month after injection).

Nine of these patients also had dyschromatopsia and the majority of cases were reported from the same center as above. In 7 of the 11 cases, the ERG changes resolved (Section 9.5.1.3).

Lens Findings

One case of lens subluxation and 1 case of lens instability were reported out of 976 patients treated with ocriplasmin (Section 9.5.2). Subluxation of the lens occurred in a 4-month old, extremely low-birth-weight premature male infant with significant ongoing medical and ocular conditions. Of note, the infant received the same ocriplasmin dose in the fellow eye 1 week later and lens subluxation did not occur. Lens instability was observed in an adult during vitrectomy 323 days following treatment with ocriplasmin in TG-MV-007. Lens evaluations were done as a part of every study visit, and no clinical signs were noted during the study or prior to the vitrectomy.

The AEs associated with ocriplasmin were all ocular and consistent with the route of administration. Patients treated with ocriplasmin had a lower incidence of disease progression and fewer vitrectomy-related complications. Although there were some notable safety findings related to visual function changes, most of these were not Serious, and were mild and transient.

Benefit-Risk

Ocriplasmin has a positive benefit-risk profile for the treatment of symptomatic VMA. In ocriplasmin-treated patients who achieve VMA resolution or FTMH closure at Day 28, there is a meaningful benefit in terms of vision and visual function. In addition, resolution of the underlying condition will halt disease progression and reduce the associated disease burden. Furthermore, patients with VMA resolution or macular hole closure are less likely to require vitrectomy and to experience the subsequent complications resulting from surgery, which is associated with a long recovery time to functional vision, the need for a second surgery (ie, cataract), and the post-operative burden on both patients and caregivers.

In those patients who do not achieve VMA resolution or macular hole closure, the risks of ocriplasmin therapy are low. The majority of adverse events are mild or moderate and transient. Patients who do not respond to ocriplasmin therapy still have the option of vitrectomy without any adverse impact on the outcome.

Ocriplasmin therapy administered as a single intravitreal injection provides an office-based treatment option. This less invasive procedure provides the first alternative to surgery and thus allows for an early intervention.

Conclusion

At present, there are no pharmacologic treatment options for patients with symptomatic VMA. The usual standard of care has been watchful waiting, often followed by vitrectomy. During watchful waiting, the patient's symptoms remain untreated, exposing the individual to risks of disease progression, complications, and in some cases, serious irreversible damage. Although highly effective, vitrectomy is a major surgical procedure that carries potentially sight-threatening risks, along with a substantial post-treatment burden for patients and their families.

Ocriplasmin is the first pharmacologic treatment for symptomatic VMA including macular hole. When successful, the anatomic result of treatment is the same as that achieved with vitrectomy. The efficacy of ocriplasmin has been demonstrated in 2 Phase 3, randomized, placebo-controlled studies. Patients treated with a single injection of ocriplasmin were significantly more likely to have resolution of VMA and closure of FTMH, and were less likely to undergo vitrectomy compared with placebo. Ocriplasmin-treated patients had clinically meaningful improvement in vision. Patients who do not achieve VMA resolution with ocriplasmin can still be offered vitrectomy, and outcomes have not been compromised in these cases.

Ocriplasmin also offers the opportunity to treat patients earlier after initial presentation, potentially leading to preservation of visual acuity and better overall long-term outcomes.

No systemic risks of intravitreal injection of ocriplasmin are expected, and none have been identified in the clinical studies to date. Most of the AEs associated with ocriplasmin administration were consistent with the intended vitreolytic activity of the drug or route of administration.

The available evidence supports a positive benefit-risk ratio. Ocriplasmin has the potential to improve the treatment of symptomatic VMA including macular hole by offering ophthalmologists and their patients a pharmacologic treatment option for this progressive and potentially sight-threatening condition.

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LIST OF ABBREVIATIONS AND ACRONYMS

ADR	adverse drug reaction
AE	adverse event
AMD	age-related macular degeneration
ANOVA	analysis of variance
BCVA	best corrected visual acuity
BLA	Biologics License Application
BMI	body mass index
CI	confidence interval
CNS	central nervous system
CRC	central reading center
DR	diabetic retinopathy
ECG	electrocardiogram
EOS	end of study
ERG	electroretinogram
ERM	epiretinal membrane
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FDA	US Food and Drug Administration
FTMH	full thickness macular hole
ILM	internal limiting membrane
IOP	intraocular pressure
MIVI-TRUST	Microplasmin for IntraVitreous Injection-Traction Release without Surgical Treatment
NEI	National Eye Institute
NLP	no light perception
nM	nanomolar
OCT	optical coherence tomography
OR	odds ratio
PD	pharmacodynamic

PK	pharmacokinetic
PVD	posterior vitreous detachment
SAE	Serious adverse event
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
US	United States
VFQ-25	25-Item Visual Functioning Questionnaire
VMA	vitreomacular adhesion
VMT	vitreomacular traction

1 INTRODUCTION

Symptomatic vitreomacular adhesion (VMA) can be a progressive, sight-threatening condition that results from incomplete separation of the vitreous from the macula.

Under normal physiologic conditions, the vitreous maintains a gel-like consistency and adheres completely to the entire surface of the retina. The consistency of the vitreous and the adhesion are both maintained by a matrix of proteins including collagen, laminin, and fibronectin, among others. As part of the normal aging process, the vitreous undergoes a gradual breakdown of this protein structure, resulting in a progressive liquefaction and subsequent separation of the vitreous from the retina, a process referred to as posterior vitreous detachment (PVD) (Figures 11 and 12) (Larsson 1985, Sebag 2005, Schneider 2011).

Figure 11. Posterior Vitreous Detachment

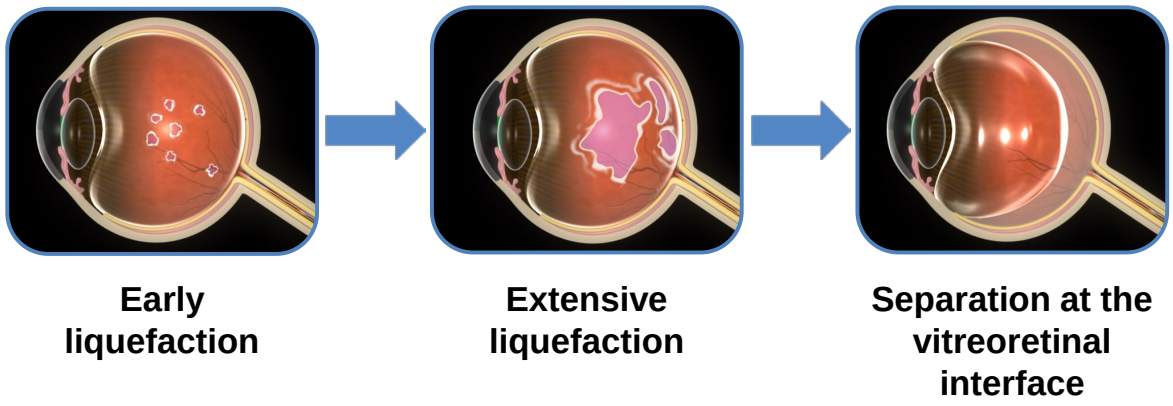
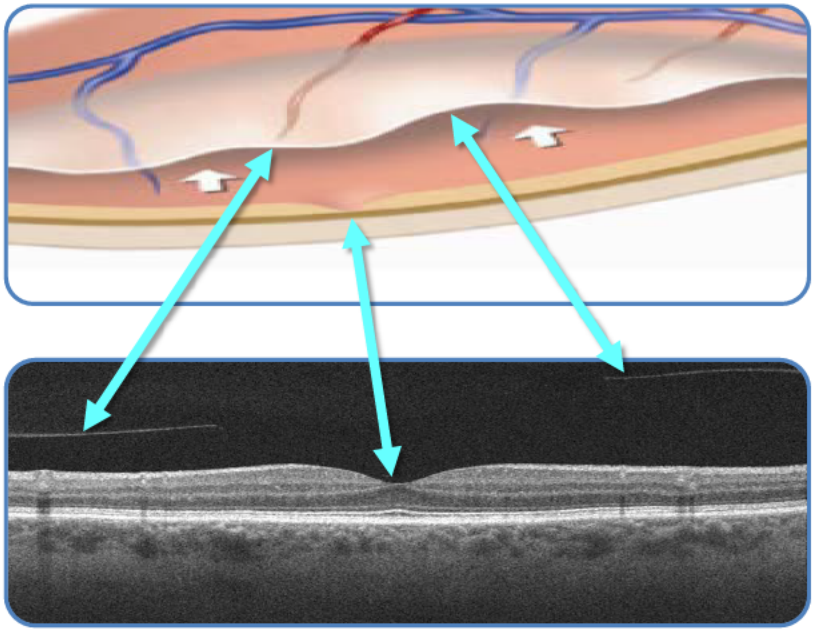


Figure 12. Normal Vitreomacular Separation

Right and left arrows show areas of complete separation of the vitreous. Middle arrow shows normal foveal depression.



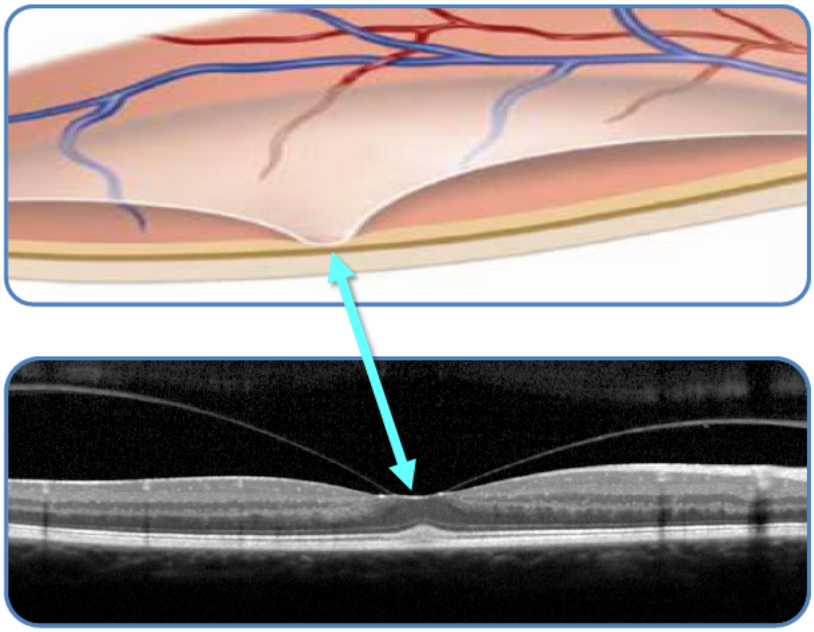
Optical coherence tomography image of the retina and vitreomacular interface.

Top panel adapted with permission from *Clinical Ophthalmology*, volume 5: Takezawa M, Toyoda F, Kambara C, et al; Clarifying the mechanism of idiopathic macular hole development in fellow eyes using spectral-domain optical coherence tomography, pages 101-108, ©2011, with permission from Dove Medical Press Ltd.

Usually, the PVD process proceeds without incident. Occasionally, however, the adhesion between the vitreous and the retina does not weaken sufficiently to allow for complete separation. Typically, the adhesion remains at sites where the bonds between the vitreous and the retina are strongest, including the macula (Schneider 2011). The macula is the primary area of the retina responsible for central vision. Adhesion at the macula is known as VMA (Figure 13).

Figure 13. Vitreomacular Adhesion

Arrow shows point of adhesion at the macula of a patient with VMA.

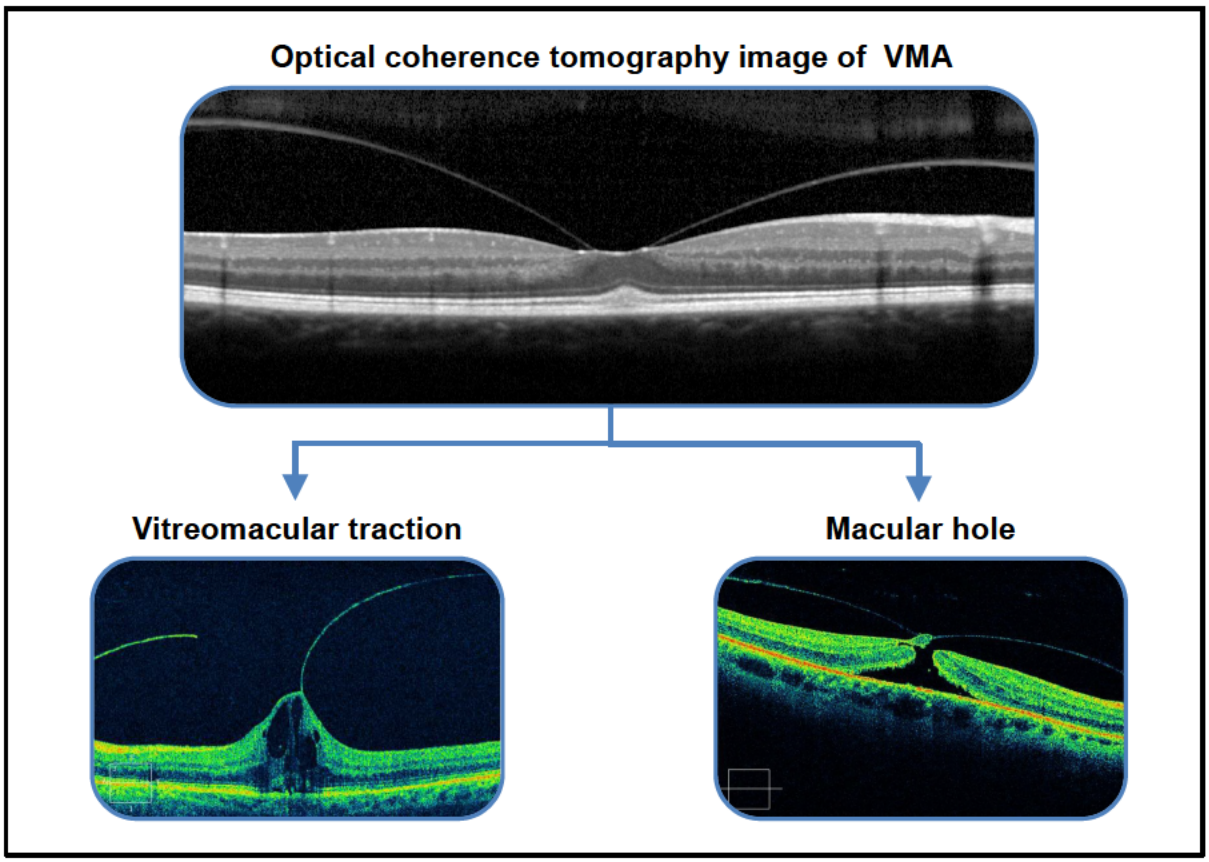


Optical coherence tomography image of the retina and vitreomacular interface.

Abbreviation: VMA, vitreomacular adhesion.
Top panel adapted with permission from *Clinical Ophthalmology*, volume 5: Takezawa M, Toyoda F, Kambara C, et al; Clarifying the mechanism of idiopathic macular hole development in fellow eyes using spectral-domain optical coherence tomography, pages 101-108, ©2011, with permission from Dove Medical Press Ltd.

Early in the disease process, VMA begins to exert tractional force at the retinal surface, which compromises the structural and functional integrity of the macula (Sebag 2004, Schneider 2011). The most common manifestations of this phenomenon are vitreomacular traction (VMT) and macular hole (Figure 14).

Figure 14. Symptomatic VMA



Patients with these conditions can present with a range of symptoms, which may include (but are not limited to) diminished visual acuity, distorted vision (metamorphopsia), and central visual field defect (blind spot). These symptoms, many of which are subjective in nature and unquantifiable, can greatly affect a patient's visual function and ability to perform normal daily activities, including reading, driving, watching television, etc.

Epidemiologic data are limited; thus, the precise incidence of symptomatic VMA has not been established. Symptomatic VMA represents a subset of the total population of patients with VMA, but most patients are asymptomatic. Use of optical coherence tomography (OCT), the established gold standard in diagnosing and managing diseases of the retina and vitreoretinal interface, is expected to lead to an increase in the number of patients diagnosed with VMA. A recent screening study using OCT found VMA present in 22% of 568 eyes, in the absence of frank symptomatology (Thomas 2012). Schwab and colleagues reported that 19% of 335 consecutive eyes had adhesions at the macula (Schwab 2012).

The limited natural history data indicate that only 10% of patients with symptomatic VMA resolve spontaneously, whereas most patients (64%) experience further deterioration in vision (Hikichi 1995, Kim 1996). Macular holes close spontaneously in only 3% to 11% of cases, and 75% of stage 2 full thickness macular holes (FTMH) progress with an increase in hole size (Am Acad Ophthalmol 2008). With continued disease progression, vision loss may become irreversible secondary to prolonged anatomic damage (Sonmez 2008). Most patients face an uncertain future of progressive vision loss and worsening symptoms.

2 THERAPEUTIC RATIONALE

There are no pharmacologic therapies for patients with symptomatic VMA. The current treatment paradigm is to observe patients ("watchful waiting") until visual symptoms deteriorate to the point that vitrectomy, the only current intervention, is justified. Vitrectomy is a major surgical procedure that entails removal of the vitreous gel of the eye and may include the peeling of retinal membranes. While highly effective in achieving separation of the vitreous from the retina, vitrectomy is not performed earlier in the disease process due to known intraoperative and post-operative risks, including retinal detachment, hemorrhage, intraocular infection, changes in intraocular pressure (IOP), macular edema, cataract formation, amongst others (Guillaubey 2007, Ramkissoon 2010, Rizzo 2010, Banker 1997, Chen 1998, Park 1995, Thompson 1996, Recchia 2010, Freeman 1997, Cheng 2001). In phakic patients, cataract formation will almost always necessitate a second operation within 2 years to replace the opacified lens (Holekamp 2005).

The recovery period after vitrectomy can be extensive. The patient may need to remain immobilized in a "head-down" position for 7 to 14 days and be dependent on caregivers. For these reasons, physicians usually monitor their patients with a watchful-waiting approach, and reserve vitrectomy until symptoms become severe.

The duration of watchful waiting is variable, as the decision to perform vitrectomy is dependent on the patient's visual needs for daily life and the rate of disease progression. During this period, patients are closely monitored with clinical examinations and OCT scans, and physicians and patients repeatedly discuss the pros and cons of intervening in view of how symptoms are affecting their personal and/or professional lives.

Among patients who undergo vitrectomy, those with less vision loss and a shorter duration of symptoms before surgery tend to have better improvement in visual acuity following surgery (Melberg 1995, Sonmez 2008). These findings suggest that earlier treatment might achieve better outcomes.

Thus, there is a pressing need for a new, earlier, and less invasive treatment option in patients with symptomatic VMA.

The objective of treatment of symptomatic VMA including macular hole is to relieve the tractional effects on the macula and restore the normal architecture of the retina. Ocriplasmin is a pharmacotherapy designed to liquefy the vitreous and cleave the bonds causing VMA, such that resolution may be achieved with minimal post-procedure burden on patients and caregivers. Ocriplasmin offers a treatment option that can be administered earlier, with the potential to reduce disease progression and the complications that can occur during watchful waiting.

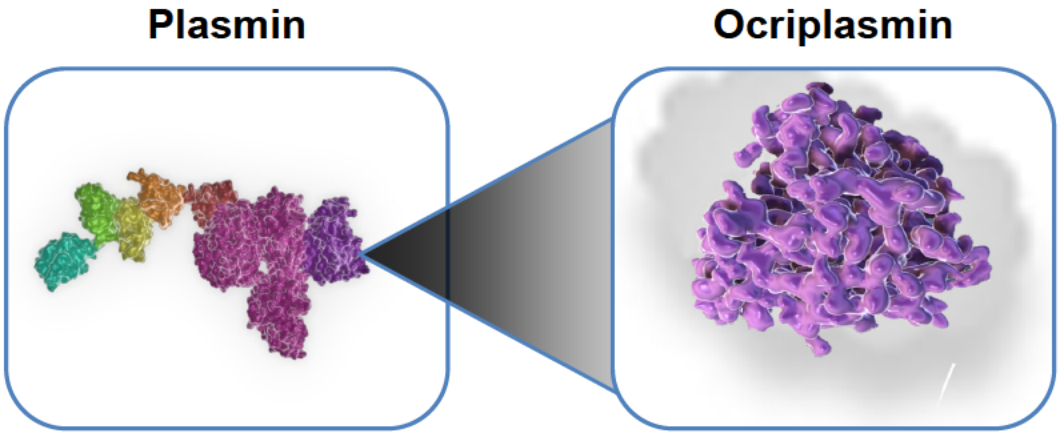
A single intravitreal injection of ocriplasmin performed in the ophthalmologist's office can achieve resolution of VMA. As the first pharmacologic treatment to offer safe and effective treatment of vitreomacular adhesion, ocriplasmin marks an important advance in the treatment of symptomatic VMA.

The proposed indication for ocriplasmin is for the treatment of symptomatic VMA including macular hole.

3 MECHANISM OF ACTION

Ocriplasmin is a recombinant truncated form of the human serine protease plasmin (molecular weight, 27.2 kDa) with retained enzymatic activity (Figure 15). The drug's enzymatic properties target the architectural components of the vitreous and the adhesion at the vitreoretinal interface, both of which are implicated in the pathogenesis of symptomatic VMA. Ocriplasmin exerts proteolytic effects on collagen, fibronectin, and laminin to produce vitreous liquefaction and detachment from the macula (Gandorfer 2004, Sebag 2012).

Figure 15. Ocriplasmin: Truncated Form of Human Plasmin



3.1 Drug Description

Ocriplasmin is obtained from microplasminogen and produced in a *Pichia pastoris* expression system by recombinant DNA technology. Ocriplasmin consists of 2 polypeptide chains containing, respectively, 19 and 230 amino acids, linked together by 2 disulfide bonds. In addition to these disulfide bonds, 4 other disulfide bonds are present. Ocriplasmin does not contain O- or N-glycosylation residues or other post-translational modifications.

The drug product is a sterile, clear, and colorless solution with no preservatives. It is contained in a single-use glass vial containing 0.5 mg of ocriplasmin in 2.5 mg/mL solution for intravitreal injection after dilution. Dilution with USP sodium chloride 9 mg/mL (0.9%) solution for injection is required. The recommended dose is 0.125 mg (125 µg), which corresponds to 0.1 mL of the diluted solution. An administration kit with all necessary components for preparation and administration of ocriplasmin intravitreal injection is being planned. The current proposed labeling has detailed instructions with diagrams to guide physicians through a stepwise process for preparation and administration.

4 DEVELOPMENT AND REGULATORY HISTORY

Among several enzymes that have been studied for their ability to modify the vitreous structure or to induce PVD, plasmin is the most promising (Schneider 2011). Plasmin is a nonspecific serine protease that has proteolytic activity against collagen, laminin, and fibronectin (Uemura 2005), important components of the vitreous structure and vitreoretinal interface responsible for

VMA (Verstraeten 1993). Autologous plasmin or plasmin derived from pooled plasma have not resulted in a useful pharmaceutical product for a number of reasons, including the instability of plasmin, the complexity of individual dose preparations, and potential safety issues. Ocriplasmin (also known as microplasmin during early development) is a truncated form of human plasmin created by recombinant DNA technology. Ocriplasmin is much more stable and is easier to prepare, compared with plasmin.

The novel mechanism of action and promising results from proof-of-concept studies encouraged ThromboGenics to join with a team of retina specialists in designing a comprehensive clinical development program to investigate the use of intravitreal ocriplasmin in the treatment of symptomatic VMA including macular hole (Gandorfer 2004, de Smet 2009).

The Phase 2 component of the ocriplasmin development program included 4 dose-ranging studies that identified an efficacious therapeutic dose of 125 µg administered via a single intravitreal injection. The Sponsor reviewed the design of the Phase 3 studies with the United States (US) Food and Drug Administration (FDA) at the End-of-Phase 2 meeting. The ensuing Phase 3 program, known as the MIVI-TRUST (Microplasmin for Intravitreous Injection-Traction Release without Surgical Treatment) program, comprised 2 randomized, placebo-controlled clinical studies, TG-MV-006 and TG-MV-007. The studies had identical treatment regimens, inclusion/exclusion criteria, therapeutic assessments, study durations, and endpoints, with the only differences being the geographic locations and the randomization allocation ratios. These 2 studies provide the clinical basis for this filing.

In addition to those who received intravitreal ocriplasmin, 97 subjects/patients received the drug via intravenous administration in doses ranging from 0.1 to 5 mg/kg in 5 studies of ocriplasmin for the treatment of vascular conditions. These studies were discontinued for commercial reasons and not for any safety concerns. The limited safety data from these studies are presented in the Biologics License Application (BLA) but not in this briefing document.

5 NONCLINICAL DEVELOPMENT

Ocriplasmin had a potent proteolytic effect on the vitreous and protein components of the vitreoretinal interface during in vitro, ex vivo, and in vivo studies. Following intravitreal injection in pig eyes, or after addition to porcine and human vitreous fluid in vitro, ocriplasmin

was quickly deactivated by the formation of an inactive complex. In systemic pharmacokinetic (PK) studies, ocriplasmin consistently and rapidly formed a complex with α_2-antiplasmin, which was cleared with a half-life ($t_{1/2}$) of 4 to 7 hours. Toxicology studies on rabbits, mini-pigs, and monkeys also demonstrated that the systemic risk to patients following intravitreal administration is negligible. These biologic and pharmacologic characteristics suggest that ocriplasmin can be considered a potent vitreolytic agent with minimal systemic exposure or risk to safety.

5.1 Safety Pharmacology

Comprehensive studies of the effects of ocriplasmin on ophthalmic neurons and glial cells following intraocular administration, and on the central nervous system (CNS), cardiovascular system, and respiratory system after intravenous administration, revealed no significant toxic effects.

Intravitreal administration of ocriplasmin in vivo to felines and rabbits was well tolerated at concentrations of 9 µg/mL and 60 µg/mL, respectively, and did not reveal safety concerns. The retina and internal limiting membrane (ILM) were well preserved, and no cellular responses by retinal neurons or glial cells were observed. Rabbit eyes that received 50 µg/eye of ocriplasmin (equivalent to 1.6 times the intended human dose) exhibited electroretinogram (ERG) changes but showed a gradual recovery of ERG amplitudes over several days; at 14 days after injection, a-wave and b-wave amplitudes were similar to those of control eyes.

Intravenous administration of 2, 6, and 10 mg/kg ocriplasmin to male rats was compared with saline and positive (30 mg/kg caffeine) controls, and showed no significant CNS effects. Infusion of 0.15 and 1.5 mg/kg ocriplasmin in anesthetized dogs did not significantly alter systolic, diastolic, or mean blood pressures, or heart rate. A dose of 15 mg/kg, which exceeds the anticipated intravitreal dose of 125 µg by about 7500-fold, produced significant reductions in blood pressure values during the intravenous infusion; these levels increased post-infusion but remained substantially lower than pre-dose values. No significant electrocardiogram (ECG) changes were observed following 0.15 and 1.5 mg/kg infusion, although half (2/4) of the dogs showed an increase of the QT and QTcV intervals at the 15 mg/kg dose. No effects on the

respiratory system were seen at any dose level, and all clinical biochemistry parameters remained unaffected, compared with pre-dose values.

In summary, ocriplasmin produced no relevant effects on key ocular tissue, the CNS, cardiovascular system, and respiratory system in studies conducted in vivo at doses orders of magnitude greater than the anticipated clinical intravitreal dose.

5.2 Nonclinical Pharmacokinetics

The intravitreal PK profile of ocriplasmin is consistent with a drug that is rapidly inactivated. Ocriplasmin in concentrations of 35 to 50 µg/mL was rapidly inactivated following intravitreal injection in, or after addition to, porcine or human vitreous fluid in vitro. After 3 hours post-injection, 6% to 23% of remaining activity was measured; after 24 hours, 2% to 10% was detected; and after 72 hours, 0.6% of the initial activity remained. A similar ocriplasmin activity profile was observed in porcine vitreous fluid following injection in ex vivo post-mortem pig eyes (study B000137) (Section 6.1.3).

Systemic PK interactions from intravitreally administered ocriplasmin are not anticipated based on rapid systemic inactivation following single injection administration of the proposed dose. Measurement of the drug's systemic PK profile indicated that ocriplasmin rapidly forms a complex with α_2-antiplasmin following intravenous administration. This inactive ocriplasmin/α_2-antiplasmin complex is metabolized through the endogenous protein catabolism pathway and subsequently cleared with a $t_{1/2}$ of several hours. The actual site of clearance in humans remains unknown. The normal plasma concentration of α_2-antiplasmin is 1000 nanomolar (nM) (Cederholm-Williams, 1981) or 1 nmol/mL of plasma. An average individual (body mass of 80 kg with normal blood volume of 72 mL/kg) has approximately 3600 mL of plasma. The 125 µg ocriplasmin dose for intravitreal administration corresponds with 4.6 nmol of active substance. Therefore, a volume of 4.6 mL of plasma has sufficient α_2-antiplasmin to neutralize all ocriplasmin, even if systemic bioavailability of the intravitreal dose was 100%. Overall, the PK studies demonstrate that systemic effects are unlikely from exposure to ocriplasmin administered intravitreally at the proposed dose of 125 µg.

5.3 Nonclinical Pharmacodynamics

Following injection into the vitreous body, ocriplasmin exerted a vitreolytic effect and prompted dissolution of the vitreoretinal interface. In vitro experiments demonstrated that ocriplasmin produced proteolytic effects on fibrin, fibrinogen, fibronectin, and to a lesser extent, collagen IV and laminin. Two independent pharmacologic experiments performed by separate laboratories, which used dynamic light scatter measurement and fluorescence in diffusion in post-mortem pig eyes, found that ocriplasmin doses ranging from 12.5 to 800 µg/eye induced alteration of the vitreous structure, ie, liquefaction of the vitreous.

Intravitreal administration of ≥125 µg of ocriplasmin in 2 post-mortem models of pig and human eyes induced a consistent and rapid induction of PVD. Additional in vivo models in rabbits and cats confirmed that PVD induction was achieved with doses between 12.5 and 250 µg/eye. In rabbits, ocriplasmin at doses of 12.5 to 250 µg/eye (equivalent to 12 to 119 µg/mL) produced cleavage at the vitreoretinal interface; in cats, the doses tested (14.5 and 25 µg/eye; equivalent to 5 and 9 µg/mL, respectively) did not cause any side effects, based on ophthalmoscopy or histopathology assessments. No evidence of compositional alteration of ILM or retina was found. Finally, an independent study in rats demonstrated that intravitreal administration of ocriplasmin (at doses resulting in concentrations between 11 and 34 µg/mL) led to a degradation of fibronectin and laminin both at the outer retina and vitreoretinal interface, along with a complete separation of the vitreous cortex from the retina without ILM damage (Chen 2009).

5.4 Toxicology

Intravitreal administration of ocriplasmin was well tolerated overall in a toxicology program in rabbits, Cynomolgus monkeys, and mini-pigs. An inflammatory response and transient ERG changes were seen in rabbits and Cynomolgus monkeys, although the incidence of vitreous cell infiltrates resolved over time (Table 1). No changes were observed in mini-pigs. Lens subluxation and gross pathologic changes related to intraocular hemorrhage were observed at doses above the intended clinical concentration in the vitreous of 29 µg/mL. No systemic toxicity was noted. Based on the intravitreal toxicology studies, the administration of ocriplasmin at a concentration of 29 µg/mL, which is equivalent to a dose of 125 µg in the human eye, was regarded as an appropriate concentration/dose in humans.

No carcinogenicity, reproductive and developmental toxicity, or immunotoxicity studies were performed, in accordance with ICH (Harmonisation for Better Health) S6 (R1) Guideline, which does not require such analyses when minimal systemic exposure is anticipated with a rapidly inactivated intravitreal agent. These approaches were confirmed with the FDA at the End-of-Phase-2 meeting.

Based on the available data, the likelihood that intravitreal administration of ocriplasmin poses a risk to patients in the proposed indication is small.

Table 1. Lowest Dose at Which Effects Are Observed After Ocriplasmin Single-Dose Administration

Species	Inflammation[a]	ERG Changes	Lens Subluxation	Gross Pathology[b]	Histological Retinal Changes[b]
Lowest concentration of observation (µg/mL)[c]					
Rabbit	**2.3 µg/mL**[d]; 2.5 µg/eye	**45 µg/mL**; 50 µg/eye	**45 µg/mL**; 50 µg/eye	**45 µg/mL**; 50 µg/eye	**45 µg/mL**; 50 µg/eye
Ratio of animal to human concentration	<0.1	1.55	1.55	1.55	1.55
Incidence	3/6 eyes	5/12 eyes	2/12 eyes	7/12 eyes	2/12 eyes
Cynomolgus monkey	**14 µg/mL**[e]; 25 µg/eye	**11 µg/mL**[f]; 20 µg/eye	**41 µg/mL**; 75 µg/eye	**108 µg/mL**; 200 µg/eye	**>108 µg/mL**; >200 µg/eye
Ratio of animal to human concentration	0.48	0.38	1.41	3.72	>3.72
Incidence	14/18 eyes	2/3 eyes	4/12 eyes	1/3 eyes	0/3 eyes
Mini-pig	**>61 µg/mL**; >125 µg/eye	**>61 µg/mL**; >125 µg/eye	**61µg/mL**; 125 µg/eye	**>61 µg/mL**; >125 µg/eye	**>61 µg/mL**; >125 µg/eye
Ratio of animal to human concentration	>2.10	>2.10	2.10	>2.10	>2.10
Incidence	0/3 eyes	0/3 eyes	1/3 eyes	0/3 eyes	0/3 eyes

Abbreviation: ERG, electroretinogram.
[a]Clinical signs of inflammation such as cyclitis, iritis, and uveitis.
[b]Pathological changes such as retinal atrophy or accumulation of macrophages in the vitreous.
[c]Data are represented in concentration per mL vitreous to allow comparison with the human dose of 125 µg/eye, corresponding to 29 µg/mL.
[d]A slight and transient infiltration of vitreous cells was observed at Day 7 by ophthalmoscopy.
[e]Inflammatory cells were detected in the anterior chamber by ophthalmoscopy on Days 2 and 7, but were no longer present at Day 15.
[f]ERG changes induced by a dose of 20 µg/eye (equivalent to 11 µg/mL) showed evidence of recovery by the last day of observation (Day 8). ERG changes induced by a dose of 25 or 125 µg/eye (equivalent to 14 or 68 µg/mL vitreous, respectively) had recovered fully by Day 55.
Data on file, ThromboGenics.

6 CLINICAL PHARMACOLOGY

The PK, pharmacodynamics (PD), safety, and tolerability of ocriplasmin were assessed in 7 studies, including 2 in vitro primary pharmacology and 1 in vitro PK study, 1 intravitreal PD and safety study, and 3 clinical PK studies. Two of those clinical studies used intravenous administration of ocriplasmin, while 1 used intravitreal injection (Table 2). No systemic biodistribution or plasma protein binding clinical studies were performed due to the very low likelihood of systemic ocriplasmin availability following intravitreal administration.

Bioavailability studies were not performed as ocriplasmin is directly injected into the vitreous. Comparative bioavailability and bioequivalence studies were not conducted because bioavailability is inestimable. In vitro-in vivo correlation studies were not conducted since sufficient analytical comparative data were generated.

Table 2. Summary of Pharmacology Studies with Ocriplasmin

Test System	Method of Administration	Testing Facility	Study Number
Primary Pharmacology Studies (in vitro)			
Enzymatic activity of ocriplasmin towards human fibrin, fibrinogen; inhibition by α_2-antiplasmin	In vitro	Katholieke Universiteit Leuven, Belgium	R04-TX-002, 2004 and Dommke et al, 2010
Enzymatic activity of ocriplasmin towards human fibrinogen, collagen type IV, gelatin, laminin and fibronectin	In vitro	ThromboGenics, NV, Leuven, Belgium	R04-TX-003, 2004
Primary Pharmacology and Safety Pharmacology Study (intravitreal administration)			
Effects of ocriplasmin on the vitreoretinal interface in human donor eyes	Intravitreal	Department of Ophthalmology, University Eye Hospital, Ludwig-Maximilians-University, Munich, Germany	Gandorfer et al, 2004
PK Studies			
Human vitreous fluid	In vitro	ThromboGenics NV, Leuven, Belgium	SR 10/mPl16/ItP, 2010
Plasma	Intravenous	Charles River Laboratories, Tranent, UK	TG-M-001
Plasma	Intravenous	Charles River Laboratories, Tranent, UK	TG-M-004
Human eyes in vivo	Intravitreal	Quality Assistance SA, Donstiennes, Belgium	TG-MV-010

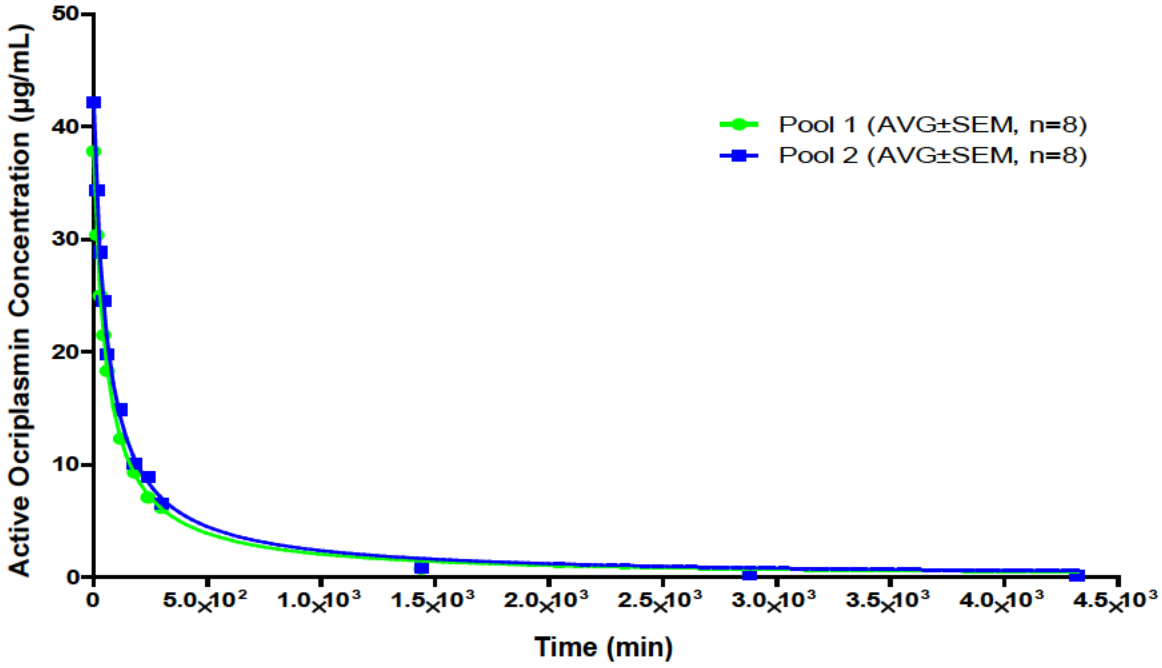
Abbreviations: PK, pharmacokinetic, UK, United Kingdom.
Data on file, ThromboGenics.

6.1 Pharmacokinetics

6.1.1 In Vitro Pharmacokinetics

The inactivation profile over time of ocriplasmin was investigated in human vitreous fluid obtained from 13 random patients undergoing vitrectomy (study SR 10mP116/ItP, 2010). Ocriplasmin was shown to be rapidly inactivated. After 72 hours of incubation at +37° C, less than 0.6% of initial active ocriplasmin was detected (Figure 16).

Figure 16. Inactivation of Ocriplasmin in Pooled Human Vitreous Fluid



Abbreviations: AVG, average; min, minutes; SEM, standard error of the mean.
Data on file, ThromboGenics.

6.1.2 In Vivo Systemic Pharmacokinetics

Ocriplasmin is quickly inactivated by α_2-antiplasmin. This was shown in an in vitro study evaluating the enzymatic properties and substrate specificity of ocriplasmin preparations, compared with natural human plasmin. The inactive ocriplasmin/α_2-antiplasmin complex was cleared from the circulation with a $t_{1/2}$ of several hours (study R04-TX-002).

In intravenous studies conducted in animals, at doses far exceeding the proposed clinical dose for intravitreal use and large enough to deplete circulating α_2-antiplasmin, the remaining ocriplasmin was cleared with a $t_{1/2}$ of approximately 1 hour. Due to the small dose of intravitreal ocriplasmin that will be used for the proposed indication, detectable levels of ocriplasmin in the systemic circulation are not anticipated. If the systemic bioavailability of the intravitreal dose were 100%, a plasma concentration of 35 ng/mL would be expected, according to data gathered in study TG-M-001; this amount was below the lower limit of quantification reported, 2.5 µg/mL. Thus, systemic bioavailability testing for intravitreal ocriplasmin is not considered relevant to the drug's potential efficacy or safety effects, and no such studies were conducted.

The systemic PK of ocriplasmin was investigated after intravenous infusion of the drug in 60 healthy male volunteers (study TG-M-001). Doses of ocriplasmin ranged from 0.5 to 3.0 mg/kg as fast infusions (over 15 minutes) to a 1.0 mg/kg fast infusion, followed by a slow infusion (over 60 minutes) of doses ranging from 1.0 to 3.0 mg/kg. Peak plasma concentrations between 0.25 and 4.25 hours were observed regardless of the administration regimen or dose. The terminal elimination $t_{1/2}$ was variable and ranged from 1.93 to 25.53 hours for all dose groups. The estimates of clearance ranged from 4.27 to 17.63 mL/h/kg. The PK parameter estimates were similar in both older (55 to 70 years) and younger (23 to 37 years) subjects.

A total exposure of 2 mg/kg is well tolerated in healthy volunteers. Notably, this exposure is >1000-fold greater than exposure that could be achieved if the entire 125 µg intravitreal dose were injected intravenously.

No intrinsic-factor PK studies were performed following intravitreal administration of 125 µg ocriplasmin, due to the lack of access to vitreous samples of patients treated without vitrectomy. As the systemic exposure of ocriplasmin following intraocular injection is minimal, PK studies during pregnancy were not performed. The effects of ocriplasmin on lactation were also not investigated. The FDA agreed that reproduction and developmental toxicity studies were not necessary if significant systemic exposure did not occur in humans following intravitreal injection of ocriplasmin. In accordance with FDA guidance, formal PK studies in patients with renal or hepatic impairment were not undertaken. No dose adjustment or special considerations for these or other populations are anticipated.

In study TG-M-001, no consistent evidence of difference in the systemic exposure or clearance of ocriplasmin between previous smokers (n = 18) and nonsmokers (n = 42) was noted. No formal drug-drug interactions or extrinsic-factor PK studies were investigated.

The PK profile of ocriplasmin in pediatric patients remains to be established.

6.1.3 In Vivo Intravitreal Pharmacokinetics

The mean ocriplasmin activity levels were measured following a single intravitreal 125 µg injection (study TG-MV-010). At 24 hours post-injection, the mean ocriplasmin activity level was 0.49 µg/mL; however, the level was below the lower limit of detection (<0.272 µg/mL) in half of the subjects (2/4) analyzed at that time point. By Day 7, activity levels in all of the subjects were similar to controls. These data correlated well with nonclinical data in porcine eyes (study B000137) (Table 3).

Table 3. Mean Ocriplasmin Levels in Vitreous Samples

Time Post-Injection	5–30 min	31–60 min	2–4 hours	24 hours	7 days
Ocriplasmin levels in TG-MV-010	12 µg/mL	8.1 µg/mL	2.6 µg/mL	0.49 µg/mL	<0.272 µg/mL[a]
Ocriplasmin levels in homogenized porcine vitreous[b] in B000137	9.3 µg/mL	4.2 µg/mL	2.8 µg/mL	ND	ND

Abbreviations: min, minutes; ND, not detected.
[a]Lower limit of detection.
[b]Concentrations as obtained from injection of 125 µg in the pig eye, most resembling the human situation.
Data on file, ThromboGenics.

6.2 Pharmacodynamics

Intravitreal injection of 125 µg and 188 µg ocriplasmin resulted in complete PVD within 30 minutes in all 9 human donor eyes in an ex vivo PD evaluation (Gandorfer 2004). Following administration of 62.5 µg ocriplasmin, electron microscopy revealed collagen fibrils and residual cortical vitreous covering the ILM. Full vitreoretinal separation was induced in a dose- and time-dependent fashion without morphologic damage to the retina.

6.3 Clinical Pharmacology Conclusions

Intravitreal injection of ocriplasmin resulted in complete PVD within 30 minutes in human donor eyes (Gandorfer 2004). Ocriplasmin is rapidly (within seconds) inactivated by α_2-antiplasmin, and the inactive ocriplasmin/α_2-antiplasmin complex is metabolized via the endogenous protein catabolism pathway. At doses far exceeding the proposed intravitreal dose of 125 µg and large enough to deplete circulating α_2-antiplasmin, any remaining ocriplasmin is eliminated with a $t_{1/2}$ of approximately 1 hour. Consequently, minimal risk of systemic effects from the use of intravitreal administration of 125 µg ocriplasmin is anticipated.

7 CLINICAL PROGRAM

ThromboGenics designed a comprehensive clinical program to assess intravitreal injection of ocriplasmin for the treatment of symptomatic VMA including macular hole, based on the promising mechanism of action and findings of earlier experiments. The results of 4 studies in the Phase 2 program, including 1 uncontrolled (TG-MV-001) and 3 controlled (TG-MV-002, TG-MV-003, and TG-MV-004) dose-ranging studies, allowed selection of a therapeutic dose of 125 µg by single intravitreal injection for Phase 3 studies. (The controlled studies are described in more detail below.) The Phase 3, randomized, placebo-controlled program comprised 2 randomized, placebo-controlled clinical studies, TG-MV-006 and TG-MV-007, which had identical treatment regimens, inclusion/exclusion criteria, assessments, study durations, and endpoints, and are the basis for this filing.

Results of the completed MIVI-TRUST studies demonstrated that a single intravitreal injection of 125 µg of ocriplasmin is superior to placebo injection for the treatment of symptomatic VMA.

Table 4 summarizes the designs, patient populations, dosing, and primary efficacy endpoints in the completed ocriplasmin Phase 2/3 studies. Additional information about the Phase 3, placebo-controlled MIVI-TRUST clinical studies follows in Sections 7.4 and 8.2.

Table 4. Description of Completed Studies in the Ocriplasmin Clinical Development Program

Study ID	Design / Control / Indication	Route and Regimen	Total Enrolment (Planned / Actual)
UNCONTROLLED STUDIES			
TG-MV-001	Phase 2 multicenter, open-label, non-controlled 6-month trial with ascending dose / exposure time in 6 sequential cohorts in patients with VMT maculopathy	Single intravitreal injection of ocriplasmin Dose / time before vitrectomy: 25 µg/1 h; 25 µg/24 h; 25 µg/7 d; 50 µg/24 h; 75 µg/24 h or 125 µg/24 h	60/61[a]
TG-MV-010	Phase 2 single center, ascending-exposure time 6-week pharmacokinetic trial prior to pars plana vitrectomy	Single intravitreal injection of ocriplasmin Dose / time before vitrectomy: 125 µg/5-30 min; 125 µg/31-60 min; 125 µg/2-4 h; 125 µg/24 h; 125 µg/7 d; no ocriplasmin treatment	36/38
CONTROLLED STUDIES			
TG-MV-002	Phase 2 multicenter, randomized, sham-injection controlled, double-masked, ascending-dose, dose-range-finding 12-month study in patients with diabetic macular edema	Single intravitreal injection of ocriplasmin (25, 75, or 125 µg) or sham injection	60/51
TG-MV-003	Phase 2 multicenter, randomized, placebo-controlled, double-masked, parallel-group, dose-ranging 6-month study in patients undergoing vitrectomy for non-proliferative vitreoretinal disease	Single intravitreal injection of ocriplasmin (25, 75, or 125 µg) or placebo	120/125
TG-MV-004	Phase 2 multicenter, randomized, sham-injection controlled, double-masked, ascending-dose, dose-range-finding 6-month trial in patients with VMT	Single intravitreal injection of ocriplasmin (75, 125, or 175 µg) or sham injection per cohort[b]	60/61
TG-MV-006	Phase 3 multicenter, randomized, placebo-controlled, double-masked 6-month study in patients with symptomatic VMA (ie, focal VMA leading to symptoms)	Single intravitreal injection of ocriplasmin 125 µg or placebo	320/326
TG-MV-007	Phase 3 multicenter, randomized, placebo-controlled, double-masked 6-month study in patients with symptomatic VMA (ie, focal VMA leading to symptoms)	Single intravitreal injection of ocriplasmin 125 µg or placebo	320/326

Abbreviations: d, days; h, hours; min, minutes; VMA, vitreomacular adhesion; VMT, vitreomacular traction.
[a]One patient withdrew consent prior to treatment and was replaced; 1 patient was allocated to 125 µg but was treated with 75 µg.
[b]In the cohort evaluating ocriplasmin 125 µg versus sham, nonresponders were eligible to receive up to 2 more open-label injections of 125 µg ocriplasmin at monthly intervals; both ocriplasmin and sham groups.
Data on file, ThromboGenics.

7.1 Study TG-MV-002

7.1.1 Study Design and Patient Population

TG-MV-002 was a Phase 2 multicenter, randomized, sham-injection controlled, double-masked, dose-finding cohort study, which evaluated the safety and preliminary efficacy of a single intravitreal injection of ocriplasmin 25, 75, or 125 µg over a 12-month period in patients with diabetic macular edema. This pilot safety study was intended to provide preliminary data to support further investigation of ocriplasmin for a possible indication of diabetic retinopathy (DR). A total of 51 patients were enrolled and treated. Following the start of the study, enrollment in the 25 µg cohort was stopped based on data from the TG-MV-004 study, which showed that higher ocriplasmin doses were well tolerated and provided better efficacy. Patients were followed through Month 12.

7.1.2 Endpoints

Efficacy assessments consisted of OCT, B-scan ultrasonography, fundus photography, fluorescein angiography, best corrected visual acuity (BCVA) using Early Treatment Diabetic Retinopathy Study (ETDRS) procedures (see Appendix A), and the National Eye Institute (NEI) 25-Item Visual Functioning Questionnaire (VFQ-25) (Appendix B). The primary efficacy endpoint was the proportion of patients with total PVD (ie, vitreous detachment to the equator), as determined by masked central reading center (CRC) evaluation at the post-injection imaging on Day 14.

7.2 Study TG-MV-003

7.2.1 Study Design and Patient Population

TG-MV-003 was a Phase 2 multicenter, randomized, double-masked, placebo-controlled, parallel-group study that evaluated the safety and efficacy of single intravitreal injections of ocriplasmin 25, 75, and 125 µg in patients with non-proliferative vitreoretinal disease without evidence of a PVD over the macula and in whom vitrectomy was indicated. A total of 125 patients were enrolled and treated. Most patients had a macular hole or VMT. Ocriplasmin was administered 7 days (±1 day) prior to pars plana vitrectomy; patients were followed for 6 months after vitrectomy.

7.2.2 Endpoints

Efficacy assessments consisted of OCT, B-scan ultrasonography, fundus photography, fluorescein angiography, and BCVA. The primary efficacy endpoint was the proportion of patients who achieved total PVD without creation of an anatomic defect (ie, retinal hole, retinal detachment), as determined by the masked investigator's visualization at the beginning of vitrectomy prior to suction or other mechanical intervention. Secondary endpoints included total PVD (by masked CRC), proportion of patients with VMT at baseline who achieved resolution without the need for vitrectomy, proportion of patients with macular hole at baseline who achieved hole closure without the need for vitrectomy, and proportion with categorical improvement in BCVA.

7.3 Study TG-MV-004

7.3.1 Study Design and Patient Population

TG-MV-004 was a Phase 2 multicenter, randomized, sham-injection controlled, double-masked, ascending-dose, dose-finding cohort study that evaluated the safety and preliminary efficacy of 4 dose regimens of intravitreal ocriplasmin in patients with idiopathic VMT, including VMT with and without FTMH. Eligible patients were sequentially assigned to 1 of 4 dose cohorts, as follows:

- 1st cohort: Injection of ocriplasmin 75 µg or sham injection
- 2nd cohort: Injection of ocriplasmin 125 µg or sham injection
- 3rd cohort: Injection of ocriplasmin 175 µg or sham injection
- 4th cohort: Injection of ocriplasmin 125 µg or sham injection, with up to 2 additional open-label ocriplasmin 125 µg injections at 1-month intervals in nonresponders (patients who showed no release of VMT on OCT or ultrasonography at 1 month post-injection; ocriplasmin and sham groups).

A total of 61 patients were enrolled and 60 were treated. Patients in each dose cohort were randomized to active treatment or sham injection in a 4:1 ratio (12 patients ocriplasmin, 3 patients sham). Patients were followed through Month 6.

7.3.2 Endpoints

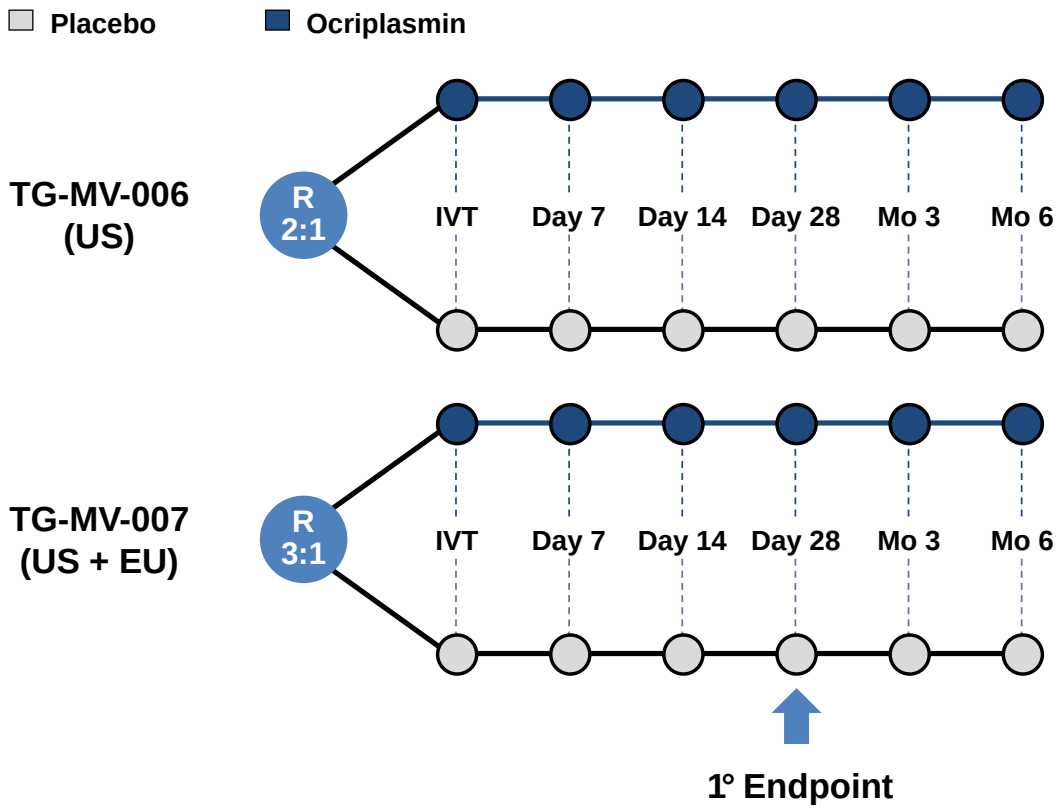
Efficacy assessments consisted of OCT, B-scan ultrasonography, and BCVA. The primary efficacy endpoint was the proportion of patients with total PVD as determined by masked CRC evaluation of B-scan ultrasound images performed at the Day 14 follow-up visit. The secondary efficacy endpoints included total PVD at other time points assessed by the CRC and investigators; resolution of the index condition; resolution of VMT; progression of PVD; the need for vitrectomy; resolution of macular edema; change in BCVA; and BCVA 5-, 10-, and 15-letter improvement.

7.4 Phase 3, Randomized, Placebo-Controlled Studies: MIVI-TRUST

7.4.1 Study Design and Patient Population

The MIVI-TRUST studies, TG-MV-006 and TG-MV-007, were both Phase 3 multicenter, randomized, placebo-controlled, double-masked, 6-month studies that investigated the safety and efficacy of a single intravitreal injection of ocriplasmin 125 µg in patients with symptomatic VMA. The 2 studies were identical in design (except for treatment allocation ratios of 2:1 in TG-MV-006 and 3:1 in TG-MV-007) and conduct (except for geography: TG-MV-006 was conducted in the US, and TG-MV-007 in the US and European Union [EU]) (Figure 17).

Figure 17. Design of Phase 3, Randomized, Placebo-Controlled MIVI-TRUST Studies: TG-MV-006 and TG-MV-007



Abbreviations: EU, European Union; IVT, intravitreal injection; Mo, month; R, randomization; US, United States.
Data on file, ThromboGenics.

To be included in the TG-MV-006 and TG-MV-007 studies, patients had to be ≥18 years of age; and to have VMA on OCT, specifically focal VMA (defined as an adhesion within a 6 mm field of the macula on OCT and surrounded by an elevation of the posterior vitreous cortex); symptoms the investigator attributed to VMA (ie, decreased visual acuity, metamorphopsia, and/or other visual complaints); BCVA of 20/25 or worse in the study eye, and BCVA of 20/800 or better in the non-study eye. At baseline, both eyes were examined (full ophthalmic exam, B-scan ultrasound, OCT, and fundus photography). If both eyes met the inclusion criteria, the eye with the worst BCVA was chosen as the study eye.

Key exclusion criteria were large diameter macular holes (>400 μm), high myopia (>8 diopter spherical correction or axial length >28 mm), or a history of retinal detachment, lens instability, proliferative DR, ischemic retinopathies, retinal vein occlusions, exudative age-related macular degeneration (AMD), and vitreous hemorrhage; ocular surgery, laser photocoagulation treatment

or intravitreal injections in the previous 3 months, and laser photocoagulation to the macula in the study eye at any time were also study exclusions.

Patients received a single intravitreal injection of ocriplasmin 125 µg or placebo. A placebo injection of vehicle was chosen instead of sham procedure to ensure identical study procedures, the double-masked design, and that any observed treatment effect in the ocriplasmin group could confidently be ascribed to the drug product.

Study treatments (placebo and ocriplasmin) were provided in glass vials with the same components except that ocriplasmin was not included in the placebo vials. Physicians used the same dilution process for ocriplasmin and placebo. Both were diluted with 0.75 mL normal saline, and 0.1 mL of the diluted solution was injected into the mid-vitreous.

The study duration was 6 months with a total of 7 visits, which took place at baseline, the day of injection, Days 7, 14, and 28, and Months 3 and 6. A full ophthalmologic examination including lens grading, B-scan ultrasound, and OCT were performed at baseline and at each visit; VFQ-25, fundus photography, and fluorescein angiograms were performed at baseline and the final visit. After the injection, the investigator performed IOP measurement and indirect ophthalmoscopic examination to exclude retinal non-perfusion or other complications.

The 6-month follow-up period was considered sufficient to evaluate efficacy and to observe for any long-term complications of a single injection.

7.4.2 Endpoints

The primary efficacy endpoint was the proportion of patients with resolution of focal VMA at Day 28 post-injection without vitrectomy, as determined by a masked CRC assessment of OCT scans. The CRC used predetermined categorical changes to assess success. Any patient who developed an anatomic defect (ie, retinal hole or retinal detachment) that resulted in the loss of vision or required additional intervention was considered as a treatment failure for the primary endpoint.

The alpha-protected secondary endpoint was the proportion of patients with total PVD (ie, vitreous detachment across the entire vitreoretinal surface) at Day 28, as determined by masked investigator-certified assessment of B-scan ultrasound.

Other secondary endpoints were the following:

- The proportion of patients with FTMH at baseline that closed without vitrectomy, as determined by the CRC
- The proportion of patients not requiring vitrectomy (patients could undergo vitrectomy after Day 28 if their condition had not improved; in addition, patients could have vitrectomy prior to Day 28 if the BCVA in the study eye worsened by ≥2 lines, at the physician's discretion)
- Achievement of ≥2 and ≥3 lines of improvement in BCVA without the need for vitrectomy (visual acuity was measured using ETDRS procedures)
- Improvement in the mean BCVA
- Improvement based on the NEI VFQ-25 (Mangione 2001) (Appendix B)

7.4.2.1 Endpoint Justification

As with vitrectomy, the objective of pharmacologic treatment of symptomatic VMA including macular hole is to relieve tractional effects at the macula, thereby resolving the underlying condition and restoring the retina to its normal anatomic and functional state. Vitrectomy has established the association between resolution of anatomic pathology and functional improvements (Ezra 2004, Hirneiss 2007, Larsson 2004, Okamoto 2010, Witkin 2010). At the End-of-Phase 2 meeting, agreement was reached with the FDA that resolution of VMA at Day 28 confirmed by OCT was clinically meaningful and acceptable as the primary endpoint for the Phase 3 studies. Total PVD at Day 28 was suggested by the FDA as a supportive secondary endpoint.

7.4.3 Statistical Methodology

The Phase 3 studies were analyzed both individually and as a combined dataset. Combined analysis was planned and documented prior to unmasking, based on the similarity in design and data collection of the 2 studies (except for randomization ratio [2:1 for TG-MV-006; 3:1 for TG-MV-007] and region). The appropriateness of the combined analysis was further confirmed when the homogeneity of odds ratios for treatment comparisons from the studies was supported by the Breslow-Day test.

Three study populations were used for the efficacy analyses, including 1) the Full Analysis Set, which included all randomized patients who received treatment, and comprised the primary population for the efficacy analyses; efficacy data were analyzed according to randomized patient-treatment group, irrespective of the treatment actually received; 2) a Modified Full Analysis Set, which excluded patients without VMA at baseline according to a masked CRC evaluation of OCT scans; and 3) a Per-Protocol Analysis Set, which comprised the Full Analysis Set but excluded patients who had a serious protocol deviation. Assuming a primary endpoint event rate of 27.5% in the 125 µg dose group and 10% in the placebo group, a sample size of 320 patients for each study was expected to achieve approximately 90% power with a 2-sided alpha of 0.05.

For categorical endpoints, the differences between treatments were evaluated using Fisher's exact test (individual studies) or the Cochran-Mantel-Haenszel test, stratified by study (combined data). For continuous endpoints, differences between treatments were evaluated using analysis of variance (ANOVA) with factor for study in the combined analysis. Logistic regression analyses were conducted as appropriate. The Breslow-Day chi-square test was used to test the hypothesis of homogeneity of odds ratios between studies.

The alpha adjustment for the individual studies was performed in the same way. The primary endpoint comparison was performed with an alpha level of 0.05 as treatment efficacy was characterized by a single primary efficacy endpoint between 2 treatment groups. The formal statistical testing of the secondary endpoint of total PVD induction at Day 28 was to be evaluated only if statistical significance ($P<0.05$) was achieved for the primary endpoint for both the Full Analysis Set and the Modified Full Analysis Set.

With the exception of the primary endpoint (resolution of VMA at Day 28) and secondary endpoint (total PVD at Day 28), analyses of the remaining secondary endpoints were considered supportive or exploratory. Results of those endpoints are described with nominal 95% confidence intervals (CIs) and nominal *P* values.

Missing data for all efficacy endpoints were replaced by the most recent observed value; the last observation carried forward method was used to impute missing data.

8 EFFICACY

This section describes the results of the controlled Phase 2 dose-ranging studies and of the Phase 3, randomized, placebo-controlled studies in patients with symptomatic VMA including macular hole. In these studies (TG-MV-006 and TG-MV-007), ocriplasmin demonstrated statistically significant and clinically meaningful efficacy in the treatment of symptomatic VMA. A single intravitreal injection of 125 µg ocriplasmin was effective in achieving the primary and secondary endpoints, resolution of VMA and induction of total PVD, respectively. Other secondary endpoints also supported the efficacy of ocriplasmin. The results were robust and consistent across endpoints, analyses, subgroups, and studies.

8.1 Controlled Dose-Finding Phase 2 Studies

8.1.1 Study TG-MV-002

This Phase 2 exploratory study was performed in patients with diabetic macular edema; consequently, the relevance of the efficacy findings to the indication of symptomatic VMA is limited. The results are described briefly here for completeness.

Total PVD rates on Day 14 and at Month 12 are shown in Table 5. In this study, ocriplasmin had no notable effect on achieving the primary endpoint (proportion of patients with total PVD), and no dose-response relationship was identified.

Table 5. Rates of Total PVD at Day 14 and Month 12 (TG-MV-002 — Full Analysis Set)

	PVD Rates, %				
	Sham-injection (n=13)	**25 µg (n=8)**	**75 µg (n=15)**	**125 µg (n=15)**	***P* value[a]**
Day 14	30.8	0	20.0	13.3	0.208
Month 12	23.1	37.5	40.0	33.3	0.502

Abbreviation: PVD, posterior vitreous detachment.
[a]Fisher's exact test; comparison of total ocriplasmin versus sham injection.
Data on file, ThromboGenics.

8.1.2 Study TG-MV-003

In the Phase 2 TG-MV-003 study in patients with non-proliferative vitreoretinal disease without evidence of a PVD over the macula and in whom vitrectomy was indicated, a dose response favoring ocriplasmin 125 µg was observed for induction of total PVD without anatomic defects, achievement of total preoperative PVD, anatomic recovery of the underlying condition without vitrectomy, and improvement in BCVA.

More patients treated with ocriplasmin than placebo achieved the primary efficacy endpoint of a total PVD without creation of an anatomic defect (ie, retinal hole, retinal detachment) based on a masked investigator's visualization at the beginning of vitrectomy prior to suction or other mechanical intervention: 21.3% (20/94) versus 10.0% (3/30), respectively (Table 6). Vitrectomy was performed 7 days after study drug injection. A dose response was observed for the proportion of patients who achieved total PVD without anatomic defect before vitrectomy (13.8%, 18.2%, and 31.3% in the ocriplasmin 25, 75, and 125 µg groups, respectively). Although the primary efficacy comparison of placebo versus total ocriplasmin was not statistically significant (*P*=0.279), the highest ocriplasmin dose approached significance (*P*=0.061).

Table 6. Summary and Analysis of Total PVD without Creation of Anatomic Defects at the Beginning of Vitrectomy[a] (TG-MV-003 — Full Analysis Set)

	Placebo (n=30)	25 µg (n=29)	75 µg (n=33)	125 µg (n=32)	Total Ocriplasmin (n=94)
Total PVD achieved without anatomic defects prior to vitrectomy, n (%)					
Yes	3 (10.0)	4 (13.8)	6 (18.2)	10 (31.3)	20 (21.3)
Treatment comparisons versus placebo					
Wald chi-square test (*P* value)[b]	—	0.796	0.447	0.107	—
Odds ratio (95% CI)[c]	—	1.24 (0.24, 6.36)	1.81 (0.39, 8.36)	3.28 (0.77, 13.95)	—
Fisher's exact test (*P* value)	—	0.706	0.479	0.061	0.279

Abbreviations: CI, confidence interval; PVD, posterior vitreous detachment.
[a]For data missing for any reason, a worst case approach (ie, presence of anatomic defect) was used; in cases where vitrectomy was not performed because the underlying pathology for which vitrectomy was originally indicated had resolved, PVD for purposes of the primary endpoint was to be based on the surgeon's assessment during the Day 7 clinic visit.
[b]*P* values are from Wald chi-square test from a logistic regression model with treatment as categorical factor.
[c]95% CI for the odds ratio of the treatment groups.
Data on file, ThromboGenics.

Induction of total PVD preoperatively was also determined by a masked CRC. By this assessment, 10.0%, 17.2%, 18.2%, and 25.0% of patients in the placebo and ocriplasmin 25, 75, and 125 µg groups, respectively, achieved total PVD. There was a dose-response trend, which was highest in the ocriplasmin 125 µg group. In patients who achieved anatomic recovery (eg, traction released in VMT, macular hole closed in patients with baseline macular hole; 3.3%, 6.9%, 12.1% and 28.1%, respectively) or anatomic recovery without the need for vitrectomy (4.8%, 6.3%, 12.9%, and 32.0%, respectively, of patients with VMT at baseline; and 0, 9.5%, 15.4%, and 30.0%, respectively, of patients with macular hole at baseline) through Day 180, the difference between the ocriplasmin 125 µg and placebo group was statistically significant for anatomic recovery (P=0.013) and anatomic recovery without the need for vitrectomy (P=0.027).

A similar dose-response was observed for measures of BCVA. The 125 µg ocriplasmin group had the highest proportion of patients with a ≥1- or ≥2-line improvement in BCVA without need for vitrectomy at Days 28, 90, and 180. The 125 µg dose ocriplasmin group also had the greatest mean improvement from baseline in BCVA at Day 28, and at Day 180, compared with the other treatment groups.

8.1.3 Study TG-MV-004

In TG-MV-004, treatment with ocriplasmin showed clinically relevant induction of total PVD, resolution of the index condition (ie, resolution of VMT in patients without baseline macular hole, and macular hole closure in patients with baseline macular hole). Optimal effect was generally observed with the 125 µg dose; no additional benefit was observed with the 175 µg dose.

The primary efficacy endpoint was the proportion of patients with total PVD, as determined by masked CRC evaluation of B-scan ultrasound images performed at the Day 14 visit. Seven of 44 (15.9%) ocriplasmin-treated patients achieved total PVD at Day 14, compared with none who received sham injection. No clear dose response was observed for this endpoint: 18.2%, 13.6%, and 18.2% of patients with ocriplasmin 75, 125, and 175 µg, respectively, achieved total PVD at Day 14 (Table 7). None of the pairwise comparisons were statistically significant.

Table 7: Proportion of Patients with Total PVD through Post-Injection Day 180 (CRC Assessment) (TG-MV-004 — Full Analysis Set)

Post-Injection Day	Sham	75 µg	125 µg	125 µg (combined cohorts[a])	175 µg
Total PVD achieved, n/N (%)					
Day 3	0/12 (0)	1/12 (8.3)	2/13 (15.4)	3/25 (12.0)	0/11 (0)
Day 7	0/12 (0)	1/12 (8.3)	2/12 (16.7)	3/23 (13.0)	1/11 (9.1)
Day 14	0/11 (0)	2/11 (18.2)	2/13 (15.4)	3/22 (13.6)	2/11 (18.2)
Day 28	0/11 (0)	2/12 (16.7)	2/11 (18.2)	4/20 (20.0)	1/11 (9.1)
Day 90[b]	0/9 (0)	2/12 (16.7)	2/13 (15.4)	N/A	1/11 (9.1)
Day 180[b]	0/9 (0)	3/12 (25.0)	2/12 (16.7)	N/A	1/10 (10)

Abbreviations: CRC, central reading center; N/A, not applicable; PVD, posterior vitreous detachment.
[a]Data for patients treated with ocriplasmin 125 µg in different patient cohorts were pooled.
[b]At post-injection Days 90 and 180, the sham group did not include 3 sham patients in the cohort that received multiple injections and extended follow-up. Similarly, data for patients treated with ocriplasmin 125 µg were not pooled after Day 28 due to the cohort that received multiple injections.
Data on file, ThromboGenics.

In line with results at Day 14, CRC grading showed a higher proportion of patients with total PVD after treatment with ocriplasmin, compared with sham controls, at the majority of time points up to Day 180. No induction of total PVD was observed for sham control patients at any time point. The proportion of patients who achieved total PVD at Day 180, as assessed by the investigator, was highest in the ocriplasmin 125 µg group.

For the purpose of the proposed indication of this submission, resolution of VMT and macular hole closure on OCT are the most relevant of the other efficacy endpoints in the TG-MV-004 study. Resolution of VMT occurred in a higher proportion of ocriplasmin-treated patients, compared with sham controls, at all time points up to Day 180, and was seen most frequently in the 125 µg group. No apparent increase in efficacy with the 175 µg dose, relative to the 125 µg dose, was noted. At Day 28, the proportion of patients with resolution of the index-condition (resolution of VMT in patients without baseline macular hole, and macular hole closure in patients with baseline macular hole) was highest in patients who received ocriplasmin 125 µg (combined cohorts: 8/25, 32.0%) and 75 µg (2/12, 16.7%) compared with those who received sham (1/12, 8.3%) or ocriplasmin 175 µg (1/11, 9.1%). Among 19 patients with macular hole at baseline, more treated with ocriplasmin 75 µg (2/3, 66.7%) or 125 µg (3/8, 37.5%) compared

with sham (1/5, 20.0%) or ocriplasmin 175 µg (0/3) had resolution of macular hole at Day 28 without vitrectomy. The BCVA improved during the post-treatment period in all treatment groups, except for the 75 µg ocriplasmin group, in which BCVA decreased after post-injection Day 28. No statistically significant differences between treatment groups in BCVA outcomes were noted.

8.1.4 Phase 2 Dose-Finding Studies: Conclusions

Results of the TG-MV-003 and TG-MV-004 studies demonstrated that the ocriplasmin 125 µg dose is well tolerated and associated with better efficacy than observed with other doses. In TG-MV-003, a dose response favoring ocriplasmin 125 µg was observed for induction of total PVD without anatomic defects, achievement of total preoperative PVD, anatomic recovery of the underlying condition without vitrectomy, and improvement in BCVA. In TG-MV-004, treatment with ocriplasmin showed clinically relevant induction of total PVD, resolution of VMT, and closure of macular hole. Optimal effect was generally observed with the 125 µg dose; no additional benefit was observed with the 175 µg dose. The uncontrolled TG-MV-001 study also found that the 125 µg dose of ocriplasmin produced the most successful release of VMT in patients with VMT maculopathy. Thus, ocriplasmin 125 µg was selected for further evaluation in the Phase 3, randomized, placebo-controlled studies.

Data from these studies support the findings of the Phase 2 studies and are described below.

8.2 Phase 3, Randomized, Placebo-Controlled Studies: MIVI-TRUST

8.2.1 Patient Disposition

The disposition and number of patients in the analysis populations for the Phase 3 studies and combined analysis are summarized in Table 8. A total of 652 patients were randomized into the Phase 3, placebo-controlled TG-MV-006 and TG-MV-007 studies and included in the combined (Full) analysis set, 188 in the placebo group and 464 in ocriplasmin 125 µg group (1 patient in TG-MV-006 who was randomized to placebo but inadvertently received ocriplasmin is included in the placebo group in the efficacy analysis [Full Analysis Set] but in the ocriplasmin group in the Safety Set). The majority of patients (93%) completed the study. The most common reasons for treatment discontinuation were withdrawal of consent and lost to follow-up.

The distribution of patients within the 3 study populations (TG-MV-006, TG-MV-007, and combined analysis) was comparable, except that more patients were randomized to receive ocriplasmin than placebo because of the different treatment allocation ratios in the 2 studies.

Table 8. Patient Disposition (TG-MV-006, TG-MV-007, and Combined Analysis)

	TG-MV-006			TG-MV-007			Combined Analysis		
	Placebo	**Ocriplasmin 125 µg**	**Total**	**Placebo**	**Ocriplasmin 125 µg**	**Total**	**Placebo**	**Ocriplasmin 125 µg**	**Total**
Patients randomized (N)	107	219	326	81	245	326	188	464	652
Completed study, n (%)	98 (91.6)	200 (91.3)	298 (91.4)	74 (91.4)	235 (95.9)	309 (94.8)	172 (91.5)	435 (93.8)	607 (93.1)
Discontinued from study, n (%)	9 (8.4)	19 (8.7)	28 (8.6)	7 (8.6)	10 (4.1)	17 (5.2)	16 (8.5)	29 (6.3)	45 (6.9)
Adverse event	2 (1.9)	2 (0.9)	4 (1.2)	0	2 (0.8)[a]	2 (0.6)	2 (1.1)	4 (0.9)	6 (0.9)
Investigator decision	0	0	0	1 (1.2)	0	1 (0.3)	1 (0.5)	0	1 (0.2)
Withdrew consent	4 (3.7)	8 (3.7)	12 (3.7)	4 (4.9)	5 (2.0)	9 (2.8)	8 (4.3)	13 (2.8)	21 (3.2)
Lost to follow-up	3 (2.8)	6 (2.7)	9 (2.8)	2 (2.5)	2 (0.8)	4 (1.2)	5 (2.7)	8 (1.7)	13 (2.0)
Death	0	3 (1.4)	3 (0.9)	0	1 (0.4)	1 (0.3)	0	4 (0.9)	4 (0.6)

Note: One patient in TG-MV-006 randomized to placebo was inadvertently treated with ocriplasmin.
[a]One patient treated with ocriplasmin in TG-MV-007 was discontinued due to metastatic brain cancer and subsequently died; this patient is not counted as discontinuing due to death in this table.
Data on file, ThromboGenics.

8.2.2 Demographics and Baseline Characteristics

Demographics and other baseline characteristics of the 652 patients randomized in the TG-MV-006 and TG-MV-007 studies are shown in Table 9. The majority of patients were female (65.8%) and most were white (92.3%). The baseline demographic and ocular characteristics in the combined dataset were generally comparable between the ocriplasmin and placebo groups. The mean age was 71.7 years (range, 18 to 97 years). At baseline, all patients in the Full Analysis Set had symptomatic VMA; 76.5% of patients had VMT with no FTMH, and 23.5% of patients had FTMH (stage 2 or worse, with concurrent VMT). Baseline ocular characteristics included epiretinal membrane (ERM) (38.7%), pseudophakia (34.5%), and DR (6.9%). In response to the following question, "If no improvement is observed in the patient's condition, do you think you would proceed to vitrectomy?" the investigators responded "Yes" for 84% of patients. The mean baseline BCVA letter score was 64.3 letters (approximately 20/50) in the combined dataset. The most notable difference between treatment groups was the greater proportion of pseudophakes in the ocriplasmin group.

Demographic and ocular characteristics were generally comparable between the individual studies, and similar to those observed in the combined analysis. Ethnicity varied between TG-MV-006 and TG-MV-007 because of the different study locations (the US for TG-MV-006, and the US and EU for TG-MV-007; ethnicity data were not collected at European sites).

Table 9. Demographic and Other Baseline Characteristics (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set)

Characteristic	TG-MV-006			TG-MV-007			Combined Analysis		
	Placebo (n=107)	Ocriplasmin (n=219)	Total (N=326)	Placebo (n=81)	Ocriplasmin (n=245)	Total (N=326)	Placebo (n=188)	Ocriplasmin (n=464)	Total (N=652)
Gender, n (%)									
Male	48 (44.9)	71 (32.4)	119 (36.5)	25 (30.9)	79 (32.2)	104 (31.9)	73 (38.8)	150 (32.3)	223 (34.2)
Female	59 (55.1)	148 (67.6)*	207 (63.5)	56 (69.1)	166 (67.8)	222 (68.1)	115 (61.2)	314 (67.7)	429 (65.8)
Age (yrs)									
Mean (SD)	71.1 (10.04)	71.5 (10.25)	71.3 (10.17)	70.2 (10.85)	72.6 (7.56)	72.0 (8.54)	70.7 (10.38)	72.1 (8.94)	71.7 (9.39)
Median	70.0	72.0	71.0	72.0	73.0	73.0	71.0	72.0	72.0
Min, max	24, 96	18, 93	18, 96	32, 97	23, 89	23, 97	24, 97	18, 93	18, 97
Race, n (%)									
White	97 (90.7)	195 (89.0)	292 (89.6)	77 (95.1)	233 (95.1)	310 (95.1)	174 (92.6)	428 (92.2)	602 (92.3)
Black	4 (3.7)	13 (5.9)	17 (5.2)	2 (2.5)	10 (4.1)	12 (3.7)	6 (3.2)	23 (5.0)	29 (4.4)
Asian	2 (1.9)	6 (2.7)	8 (2.5)	2 (2.5)	2 (0.8)	4 (1.2)	4 (2.1)	8 (1.7)	12 (1.8)
Other	4 (3.7)	5 (2.3)	9 (2.8)	0	0	0	4 (2.1)	5 (1.1)	9 (1.4)
Ethnicity, n (%)									
Non-Hispanic (US)	98 (91.6)	204 (93.2)	302 (92.6)	32 (39.5)	103 (42.0)	135 (41.4)	130 (69.1)	307 (66.2)	437 (67.0)
Hispanic (US)	9 (8.4)	15 (6.8)	24 (7.4)	4 (4.9)	8 (3.3)	12 (3.7)	13 (6.9)	23 (5.0)	36 (5.5)
Not specified (non-US)	0	0	0	45 (55.6)	134 (54.7)	179 (54.9)	45 (23.9)	134 (28.9)	179 (27.5)

Characteristic	TG-MV-006			TG-MV-007			Combined Analysis		
	Placebo (n=107)	**Ocriplasmin (n=219)**	**Total (N=326)**	**Placebo (n=81)**	**Ocriplasmin (n=245)**	**Total (N=326)**	**Placebo (n=188)**	**Ocriplasmin (n=464)**	**Total (N=652)**
Baseline Diagnosis,[a] n (%)									
FTMH	32 (29.9)	57 (26.0)	89 (27.3)	15 (18.5)	49 (20.0)	64 (19.6)	47 (25.0)	106 (22.8)	153 (23.5)
VMT (including DR)	75 (70.0)	162 (74.0)	237 (72.7)	66 (81.5)	196 (80.0)	262 (80.4)	141 (75.0)	358 (77.2)	499 (76.5)
Baseline Study Eye Ocular Characteristics,[b] n (%)									
ERM	35 (32.7)	86 (39.3)	121 (37.1)	33 (40.7)	98 (40.0)	131 (40.2)	68 (36.2)	184 (39.7)	252 (38.7)
Pseudophakic	29 (27.1)	91 (41.6)*	120 (36.8)	24 (29.6)	81 (33.1)	105 (32.2)	53 (28.2)	172 (37.1)*	225 (34.5)
DR	7 (6.5)	12 (5.5)	19 (5.8)	8 (9.9)	18 (7.3)	26 (8.0)	15 (8.0)	30 (6.5)	45 (6.9)
Type (Diameter) of Focal VMA,[c] n/N (%)									
>1500µm	19/99 (19.2)	47/207 (22.7)	66/306 (21.6)	22/77 (28.6)	55/233 (23.6)	77/310 (24.8)	41/176 (23.3)	102/440 (23.2)	143/616 (23.2)
≤1500µm	74/99 (74.7)	145/207 (70.0)	219/306 (71.6)	49/77 (63.6)	169/233 (72.5)	218/310 (70.3)	123/176 (69.9)	314/440 (71.4)	437/616 (70.9)
Could not determine	6/99 (6.1)	15/207 (7.2)	21/306 (6.9)	6/77 (7.8)	9/233 (3.9)	15/310 (4.8)	12/176 (6.8)	24/440 (5.5)	36/616 (5.8)
Expected Need for Vitrectomy,[d] n (%)									
Yes	85 (79.4)	174 (79.5)	259 (79.4)	67 (82.7)	222 (90.6)	289 (88.7)	152 (80.9)	396 (85.3)	548 (84.0)
No	22 (20.6)	44 (20.1)	66 (20.2)	14 (17.3)	23 (9.4)	37 (11.3)	36 (19.1)	67 (14.4)	103 (15.8)
Missing	0	1 (0.5)	1 (0.3)	0	0	0	0	1 (0.2)	1 (0.2)
Total PVD at Baseline, n (%)									
Yes	0	1 (0.5)	1 (0.3)	0	0	0	0	1 (0.2)	1 (0.2)
No	107 (100.0)	218 (99.5)	325 (99.7)	81 (100.0)	245 (100.0)	326 (100.0)	188 (100.0)	463 (99.8)	651 (99.8)

Characteristic	TG-MV-006			TG-MV-007			Combined Analysis		
	Placebo (n=107)	**Ocriplasmin (n=219)**	**Total (N=326)**	**Placebo (n=81)**	**Ocriplasmin (n=245)**	**Total (N=326)**	**Placebo (n=188)**	**Ocriplasmin (n=464)**	**Total (N=652)**
BCVA (Letter Score)									
Mean (SD)	65.3 (9.83)	64.5 (10.86)	64.8 (10.53)	64.9 (11.58)	63.4 (13.69)	63.8 (13.20)	65.1 (10.59)	63.9 (12.43)	64.3 (11.94)
Median	67.0	67.0	67.0	66.5	67.0	67.0	67.0	67.0	67.0
Min, max	38, 82	20, 85	20, 85	9, 82	8, 88	8, 88	9, 82	8, 88	8, 88
Macular Hole Width,[e] n/N (%)									
Width >250 µm	16/32 (50.0)	27/56 (48.2)	43/88 (48.9)	6/15 (40.0)	30/49 (61.2)	36/64 (56.3)	22/47 (46.8)	57/105 (54.3)	79/152 (52.0)
Width ≤250 µm	16/32 (50.0)	29/56 (51.8)	45/88 (51.1)	9/15 (60.0)	19/49 (38.8)	28/64 (43.8)	25/47 (53.2)	48/105 (45.7)	73/152 (48.0)

Abbreviations: BCVA, best corrected visual acuity; CRC, central reading center; DR, diabetic retinopathy; ERM, epiretinal membrane; FTMH, full thickness macular hole; OCT, optical coherence tomography; PVD, posterior vitreous detachment; SD, standard deviation; US, United States; VMA, vitreomacular adhesion; VMT, vitreomacular traction.

[*]Denotes a statistically significant difference between treatment groups.

[a]Based on CRC review of pretreatment OCT; all cases other than FTMH were considered to be VMT.

[b]Patients could have had >1 baseline ocular characteristic.

[c]Percentages are based on total number of patients in the Modified Full Analysis Set.

[d]Yes/no answer to question asked of the investigator prior to randomization: "If no improvement is observed in the patient's condition, do you think you would proceed to vitrectomy?"

[e]Macular hole width was not reported for 1 patient in TG-MV-006.

8.2.3 Primary Endpoint: Resolution of VMA at Day 28

In both TG-MV-006 and TG-MV-007, ocriplasmin 125 µg was superior to placebo in achieving the primary efficacy endpoint, resolution of focal VMA at post-injection Day 28, as determined by masked CRC evaluation of OCT scans (Figure 18).

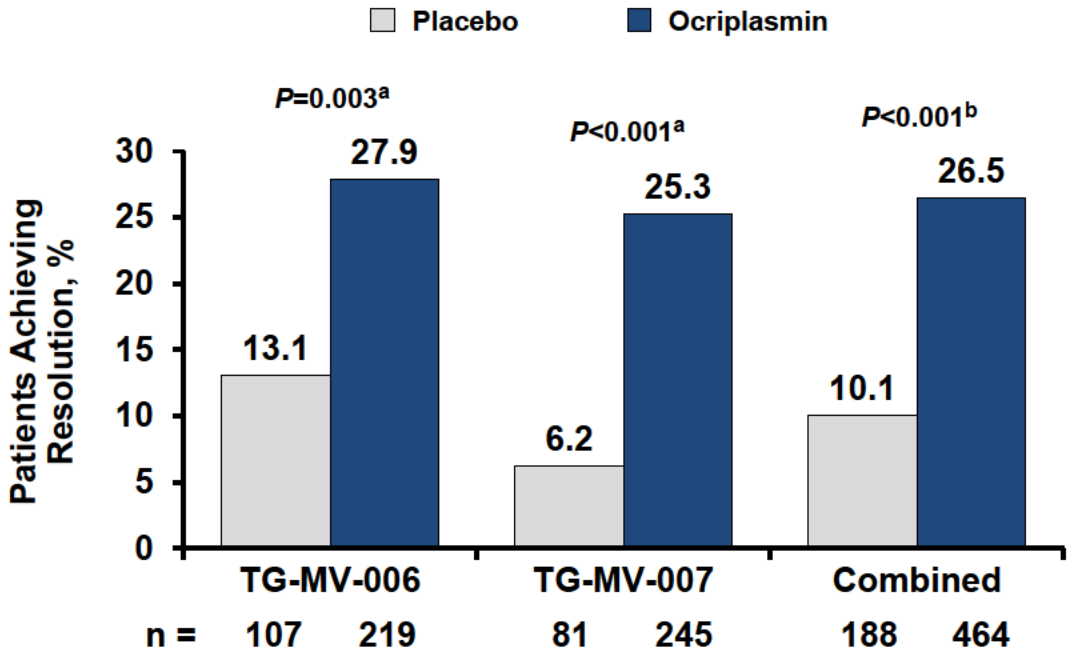
Significantly more patients in the Full Analysis Set treated with ocriplasmin had resolution of VMA at Day 28, compared with placebo: 27.9% versus 13.1%, respectively, in TG-MV-006 (absolute difference between treatment groups of 14.8% [95% CI: 6.0%–23.5%], P=0.003); and 25.3% versus 6.2% in TG-MV-007 (absolute difference of 19.1% [95% CI: 11.6%–26.7%], P<0.001).

The placebo event rate of VMA resolution in TG-MV-006 was approximately twice that observed in TG-MV-007. This may have been due to the greater number of patients with macular holes (29.9% versus 18.5%), fewer patients with ERM (32.7% versus 40.7%), or greater proportion of patients with a VMA diameter ≤1500 µm (74.7% versus 63.6%) at baseline in TG-MV-006 versus TG-MV-007, respectively (see Table 9). All of these factors can affect VMA resolution. Despite the difference in placebo event rates, ocriplasmin treatment resulted in higher response rates than placebo in both of the studies. The similarity of odds ratios between the 2 Phase 3, placebo-controlled studies was supported by non-significant P values of the Breslow-Day homogeneity test.

In the combined analysis, rates of VMA resolution at Day 28 were 26.5% with ocriplasmin versus 10.1% with placebo (absolute difference of 16.4% [95% CI: 10.5–22.3], P<0.001).

Geographic region (ie, US versus EU) was not found to be a predictor of achieving VMA resolution (or for secondary endpoints including total PVD, macular hole closure, vitrectomy rate, or categorical BCVA improvement).

Figure 18. Primary Efficacy Endpoint: Proportion of Patients with VMA Resolution at Day 28 (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set)



Abbreviation: VMA, vitreomacular adhesion.
[a]Fisher's exact test; [b]Cochran-Mantel-Haenszel test, stratified by study.
Data on file, ThromboGenics.

Similar results to those obtained in the Full Analysis Set were observed in the Modified Full Analysis Set and the Per-Protocol Set (Table 10). For each dataset, the proportion of patients who achieved VMA resolution at Day 28 regardless of the creation of an anatomic defect was similar to that of patients who achieved VMA resolution without creation of an anatomic defect.

The treatment effect observed in the combined analysis was confirmed using logistic regression analysis. In the model adjusted for baseline covariates, study treatment had a significant effect on the proportion of patients who achieved VMA resolution at Day 28, both in the Full Analysis Set ($P<0.001$, odds ratio [OR]: 6.008 [95% CI: 3.158–11.433]) and the Modified Full Analysis Set ($P<0.001$, OR: 6.008 [95% CI: 3.158–11.432]).

Table 10. Proportion of Patients with VMA Resolution at Day 28 (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set, Modified Full Analysis Set, and Per-Protocol Set)

	TG-MV-006				TG-MV-007				Combined Analysis			
	PL	Ocriplasmin 125 µg	Difference (95% CI)[a]	*P* value[b]	PL	Ocriplasmin 125 µg	Difference (95% CI)[a]	*P* value[b]	PL	Ocriplasmin 125 µg	Difference (95% CI)[a]	*P* value[b]
Full Analysis Set												
N	107	219			81	245			188	464		
n (%)	14 (13.1)	61 (27.9)	14.8 (6.0, 23.5)	0.003	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	<0.001	19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)	<0.001
Modified Full Analysis Set												
N	99	207			77	233			176	440		
n (%)	14 (14.1)	61 (29.5)	15.3 (6.1, 24.6)	0.004	5 (6.5)	62 (26.6)	20.1 (12.2, 28.0)	<0.001	19 (10.8)	123 (28.0)	17.2 (10.9, 23.4)	<0.001
Per-Protocol Set												
N	94	189			71	214			165	403		
n (%)	14 (14.9)	58 (30.7)	15.8 (6.0, 25.5)	0.004	4 (5.6)	56 (26.2)	20.5 (12.6, 28.5)	<0.001	18 (10.9)	114 (28.3)	17.4 (10.9, 23.9)	<0.001

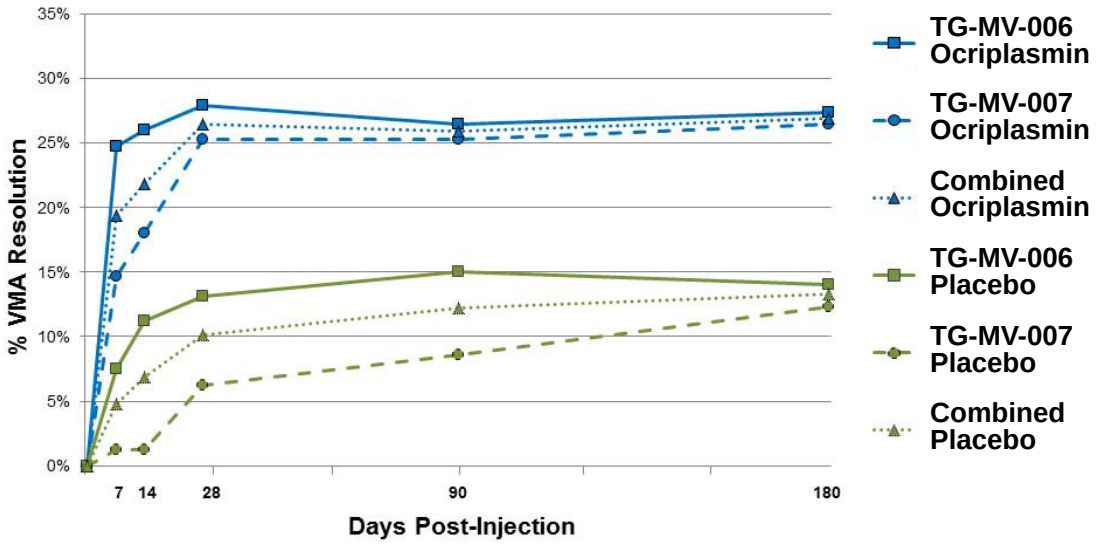
Abbreviations: CI, confidence interval; PL, placebo; VMA, vitreomacular adhesion.
[a]The (absolute) difference and CIs between treatment groups are based on the proportion of successes.
[b]*P* value from Fisher's exact test for individual studies; *P* value from Cochran-Mantel-Haenszel test for the combined analysis, stratified by study.
Data on file, ThromboGenics.

8.2.3.1 VMA Resolution by Study Visit

The proportion of patients who achieved resolution of VMA was statistically significantly higher in the ocriplasmin group compared with the placebo group at all post-injection study visits through Month 6 ($P \leq 0.024$, $P \leq 0.009$, and $P < 0.001$ in TG-MV-006, TG-MV-007, and by combined analysis, respectively) (Figure 19). Most patients in the ocriplasmin group who achieved VMA resolution did so by the first post-injection visit on Day 7 (90/125, 72.0%), as compared with 9 of 25 (36.0%) patients in the placebo group, by combined analysis.

Multivariate logistic regression analysis adjusted for baseline covariates confirmed the significance of the treatment effect observed at Month 6 in the combined analysis ($P < 0.001$, OR: 3.211 [95% CI: 1.874, 5.502]).

Figure 19. Proportion of Patients with VMA Resolution through Month 6 (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set)

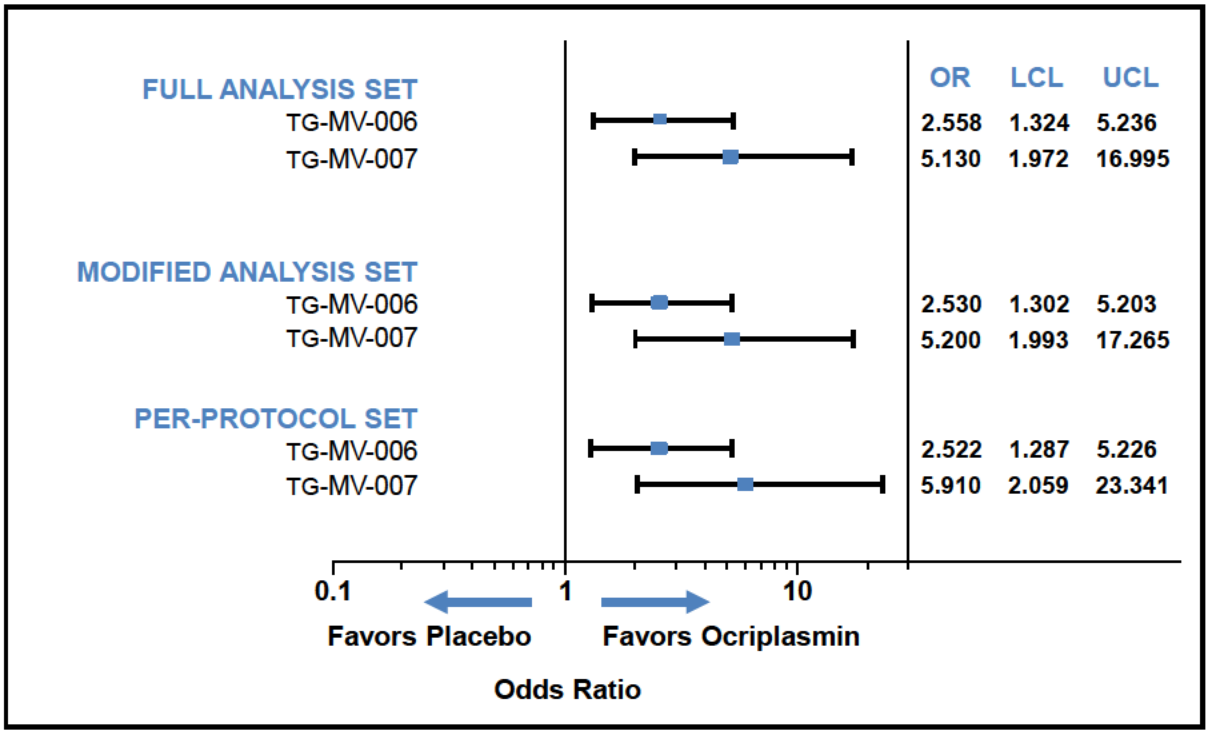


Abbreviation: VMA, vitreomacular adhesion.
At all post-injection days, $P \leq 0.024$ in TG-MV-006, $P \leq 0.009$ in TG-MV-007, $P < 0.001$ in combined analysis; *P* value from Fisher's exact test for individual studies; *P* value from Cochran-Mantel-Haenszel test for the combined analysis, stratified by study.
Data on file, ThromboGenics.

8.2.3.2 Sensitivity Analysis

Uniformity of results between the individual studies further justified the combined analysis of data from the 2 studies (Figure 20). The sensitivity analysis also demonstrated that all analyses of the comparison between ocriplasmin 125 µg and placebo were statistically significant.

Figure 20. Odds Ratios (and 95% CIs) of the Comparison of Ocriplasmin versus Placebo for VMA Resolution at Day 28 (All Analysis Sets)



Abbreviations: CI, confidence interval; LCL, lower confidence limit; OR, odds ratio; UCL, upper confidence limit; VMA, vitreomacular adhesion.
Data on file, ThromboGenics.

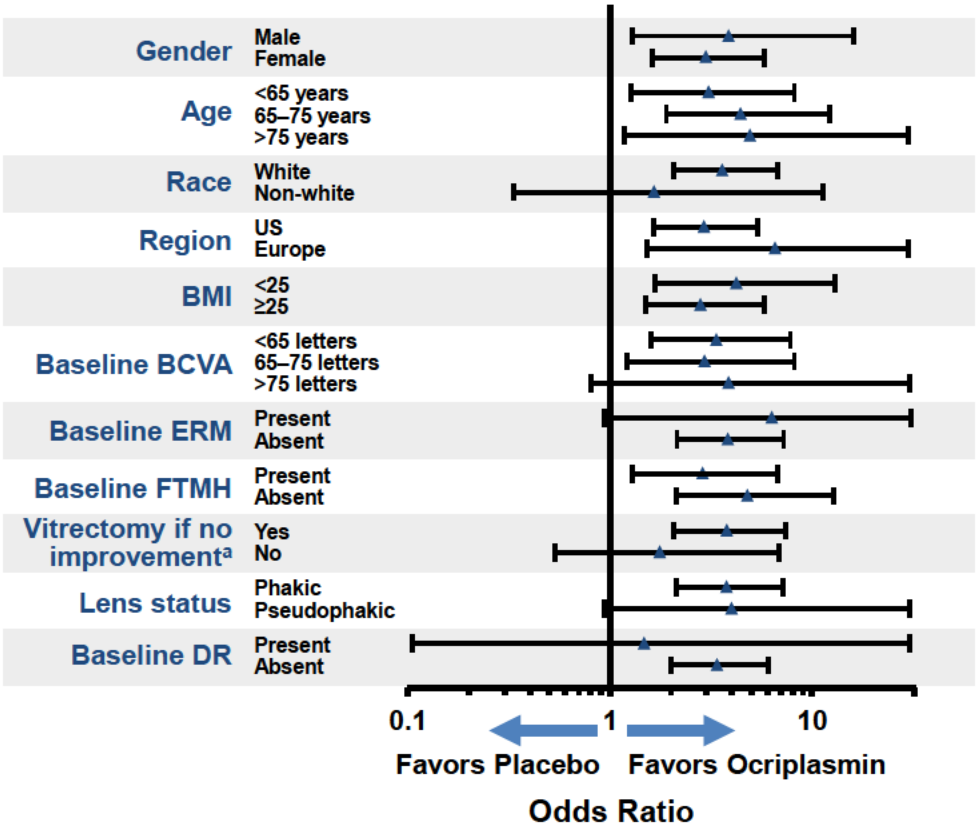
Logistic regression analyses were conducted to evaluate the effects of covariates on the efficacy endpoints. Demographic covariates evaluated include age (<65 versus ≥65 years; <75 versus ≥75 years; and <65 years, 65−75 years, and >75 years), gender, race (white versus non-white), body mass index (BMI) (<25 kg/m^2 versus ≥25 kg/m^2), and geographic region (non-US versus US). Baseline covariates evaluated included ERM status (present versus absent), type (diameter) of focal VMA (≤1500 µm versus >1500 µm), FTMH status (present versus absent), lens status (phakic versus pseudophakic), DR status (present versus absent), expected need for vitrectomy (needed versus not needed), and BCVA at baseline (<65 letters, 65−75 letters, and >75 letters).

In this analysis, baseline characteristics identified as predictors of response to treatment in the Full Analysis Set were age, ERM status, FTHM status, lens status, and type (diameter) of focal VMA. Patients more likely to respond were those who at baseline were younger (<65 versus ≥65 years of age) (OR: 4.278 [95% CI: 2.075–8.821], P<0.001), with no ERM (versus with ERM)

(OR: 0.241 [95% CI: 0.126–0.458], *P*<0.001), with FTMH (versus no FTMH) (OR: 2.053 [95% CI: 1.126–3.742], *P*=0.019), phakic (versus pseudophakic) (OR: 2.824 [95% CI: 1.536–5.192], *P*<0.001), or with focal VMA ≤1500 µm (versus >1500 µm) (OR: 4.918 [95% CI: 1.955–12.372], *P*<0.001).

In the subgroup analyses, treatment differences in favor of ocriplasmin 125 µg for achieving the primary endpoint (VMA resolution at Day 28) were observed across all subgroups identified by various baseline demographic and ocular characteristics (Figure 21).

Figure 21. Odds Ratios for the Subgroup Analyses of VMA Resolution at Day 28 (Combined Analysis: Subgroup Analysis)



Abbreviations: BMI, body mass index; BCVA, best corrected visual acuity; DR, diabetic retinopathy; ERM, epiretinal membrane; FTMH, full thickness macular hole; VMA, vitreomacular adhesion.
[a]Yes/no answer to the question asked of the investigator prior to randomization: "If no improvement is observed in this patient's condition, do you think you would proceed to vitrectomy?"
Data on file, ThromboGenics.

8.2.4 Secondary Endpoints

8.2.4.1 Patients with Total Posterior Vitreous Detachment at Day 28 (Alpha-Protected Endpoint)

The proportion of patients with total PVD at Day 28 was determined by masked investigator assessment of B-scan ultrasound images. In each of the studies and by combined analysis, significantly more patients treated with ocriplasmin 125 µg than placebo achieved this endpoint in the Full Analysis Set: 16.4% versus 6.5%, respectively, in TG-MV-006 (absolute difference between treatment groups of 9.9% [95% CI: 3.1%–16.7%], P=0.014); and 10.6% versus 0 in TG-MV-007 (absolute difference of 10.6% [95% CI: 6.8%–14.5%], P<0.001) (Figure 22). The similarity of odds ratios between the 2 studies was supported by non-significant P values of the Breslow-Day homogeneity test.

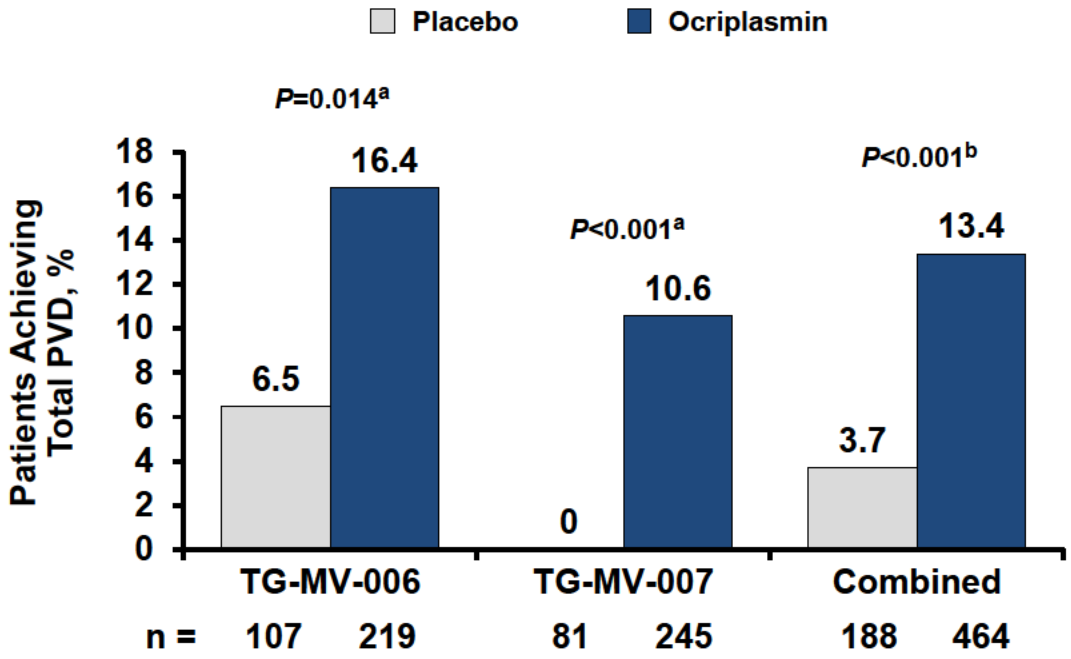
Similar results to those obtained in the Full Analysis Set were observed in the Modified Full Analysis Set and the Per-Protocol Set (Table 11).

Although the proportions of patients in the placebo and ocriplasmin groups with total PVD at Day 28 were numerically higher in TG-MV-006 than in TG-MV-007, the absolute treatment differences were similar between the 2 studies.

In the combined (Full) analysis set, 13.4% versus 3.7% of patients treated with ocriplasmin and placebo, respectively, had total PVD at Day 28 (absolute difference of 9.6% [95% CI: 5.5%–13.8%], P<0.001).

The treatment effect in the combined (Full) analysis set was confirmed using logistic regression analysis. In the model adjusted for baseline covariates, study treatment had a significant effect on the proportion of patients in the combined (Full) analysis set who achieved total PVD at Day 28 (P<0.001, OR: 5.406 [95% CI: 2.174–13.446]).

Figure 22. Proportion of Patients with Total PVD at Day 28 (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set)



Abbreviation: PVD, posterior vitreous detachment.
[a]Fisher's exact test; [b]Cochran-Mantel-Haenszel test, stratified by study.
Data on file, ThromboGenics.

Table 11. Proportion of Patients with Total PVD at Day 28 (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set, Modified Full Analysis Set, and Per-Protocol Set)

	TG-MV-006				TG-MV-007				Combined Analysis			
	PL	Ocriplasmin 125 µg	Difference (95% CI)[a]	*P* value[b]	PL	Ocriplasmin 125 µg	Difference (95% CI)[a]	*P* value[b]	PL	Ocriplasmin 125 µg	Difference (95% CI)[a]	*P* value[b]
Full Analysis Set												
N	107	219			81	245			188	464		
n (%)	7 (6.5)	36 (16.4)	9.9 (3.1, 16.7)	0.014	0	26 (10.6)	10.6 (6.8, 14.5)	<0.001	7 (3.7)	62 (13.4)	9.6 (5.5, 13.8)	<0.001
Modified Full Analysis Set												
N	99	207			77	233			176	440		
n (%)	6 (6.1)	30 (14.5)	8.4 (1.7, 15.1)	0.037	0	24 (10.3)	10.3 (6.4, 14.2)	0.001	6 (3.4)	54 (12.3)	8.9 (4.8, 12.9)	<0.001
Per-Protocol Set												
N	94	189			71	214			165	403		
n (%)	6 (6.4)	28 (14.8)	8.4 (1.4, 15.5)	0.051	0	24 (11.2)	11.2 (7.0, 15.4)	<0.001	6 (3.6)	52 (12.9)	9.3 (4.9, 13.6)	<0.001

Abbreviations: CI, confidence interval; PL, placebo; PVD, posterior vitreous detachment.
[a]The (absolute) difference and CIs between treatment groups are based on the proportion of successes.
[b]*P* value from Fisher's exact test for individual studies; *P* value from Cochran-Mantel-Haenszel test for the combined analysis, stratified by study.
Data on file, ThromboGenics.

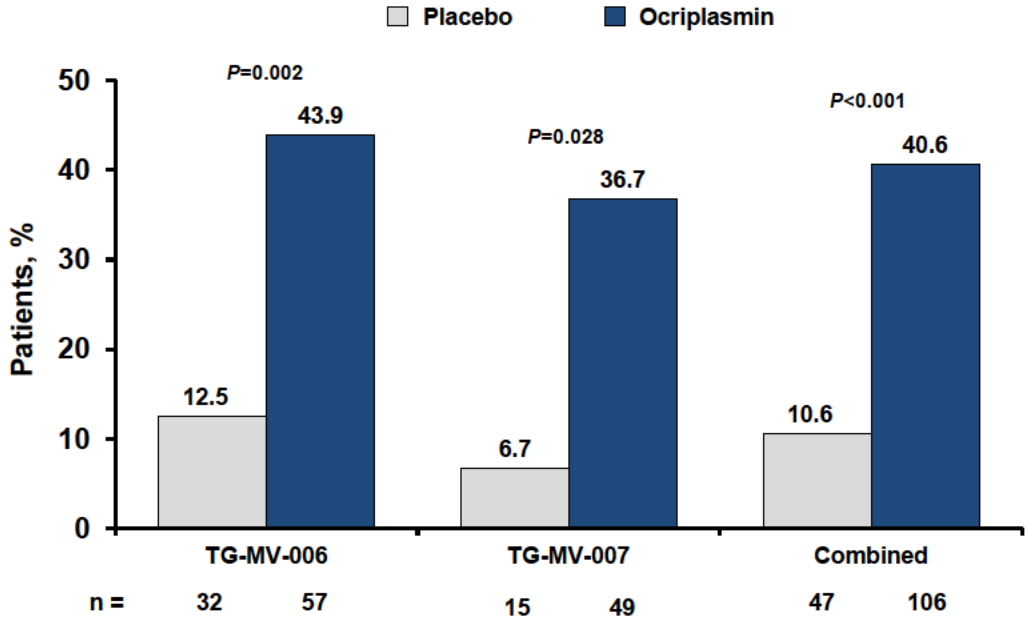
8.2.4.2 Macular Hole Closure, without Vitrectomy

At baseline in the combined (Full) analysis set, 153 patients had a macular hole, 106 in the ocriplasmin group and 47 in the placebo group (see Table 9).

In the individual TG-MV-006 and TG-MV-007 studies and by combined analysis, more ocriplasmin- than placebo-treated patients had non-surgical macular hole closure at Day 28 (Figure 23). In the combined analysis, the absolute difference between treatment groups at Day 28 was 29.9% (95% CI: 17.1%–42.8%, $P<0.001$).

The treatment effect observed in the overall analysis was confirmed using logistic regression analysis. In the model adjusted for baseline covariates, study treatment had a notable effect on the proportion of patients who achieved pharmacologic closure of a macular hole at Day 28 ($P<0.001$, OR: 8.416 [95% CI: 2.848–24.864]).

Figure 23. Proportion of Patients with Macular Hole Closure[a] at Day 28 (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set)

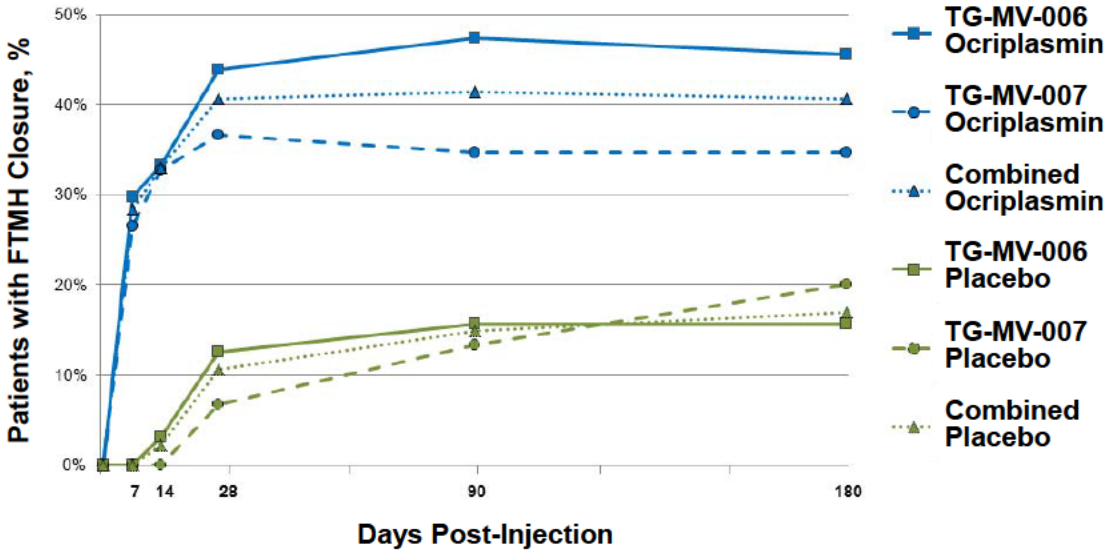


[a]Without vitrectomy.
Note: *P* value from Fisher's exact test for individual studies; *P* value from Cochran-Mantel-Haenszel test for the combined analysis, stratified by study.
Data on file, ThromboGenics.

The proportion of patients in the individual studies and the combined analysis who achieved macular hole closure (without vitrectomy) was higher in the ocriplasmin group at each post-

injection study visit through Month 6, compared with placebo. The difference between the ocriplasmin and placebo groups was statistically significant at all time points, except at Months 3 and 6 in the TG-MV-007 study (Figure 24). The majority (30/44 [68.2%], in combined analysis) of patients in the ocriplasmin group who reached this endpoint did so by Day 7, compared with none of the placebo-treated patients.

Figure 24. Proportion of Patients with Macular Hole Closure[a] by Study Visit (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set)



Abbreviation: FTMH, full thickness macular hole.
[a]Without vitrectomy.
Note: $P \leq 0.005$ in TG-MV-006, at all post-injection days; $P \leq 0.028$ in TG-MV-007, up to Day 28 (included); $P \leq 0.004$ in combined analysis, at all post-injection days; *P* value from Fisher's exact test for individual studies; *P* value from Cochran-Mantel-Haenszel test for the combined analysis, stratified by study.
Data on file, ThromboGenics.

In patients in both treatment groups who did not achieve macular hole closure after intravitreal treatment and subsequently had a vitrectomy, more than 90% in both treatment groups had successful closure of a macular hole after vitrectomy, a rate comparable to that reported in the literature (D'Souza 2011). Visual outcome (ie, change in BCVA from baseline) in this cohort was at least as favorable in the ocriplasmin as in the placebo group. These factors indicate that ocriplasmin therapy does not compromise future surgical treatment in patients who do not achieve macular hole closure after ocriplasmin treatment.

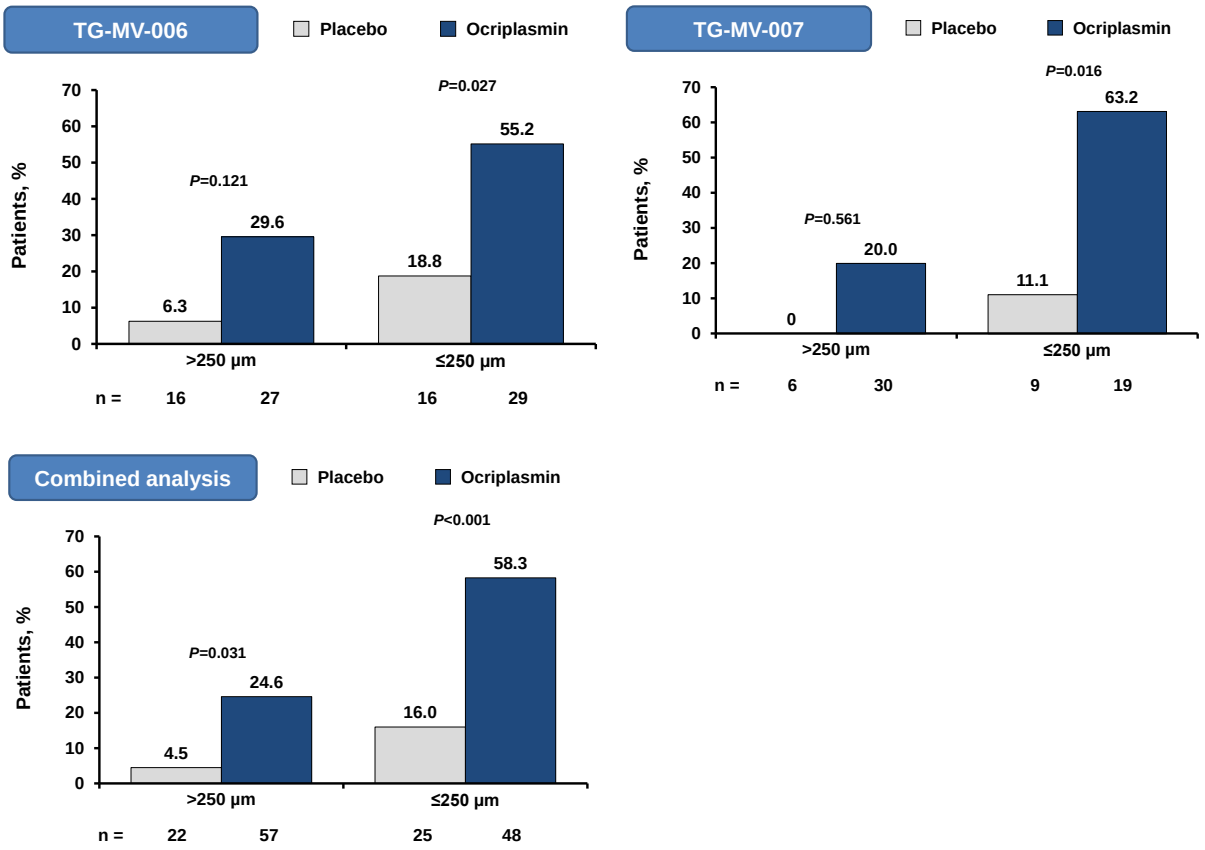
8.2.4.2.1 Macular Hole Closure According to Hole Width at Baseline

At baseline, the percentage of patients with a macular hole width ≤250 μm was slightly lower in the ocriplasmin group (45.7%), and with a macular hole width >250 μm was slightly higher in the ocriplasmin group (54.3%), compared with the placebo group in the combined (Full) dataset (see Table 9).

Patients with less advanced disease would be expected to have more successful treatment outcomes, and results from the individual Phase 3 studies and the combined dataset show that patients with a baseline macular hole width ≤250 μm who were treated with ocriplasmin were more likely to achieve macular hole closure at Day 28, compared with placebo (Figure 25).

In the combined (Full) analysis set in patients with a baseline macular hole width ≤250 μm, 58.3% of patients treated with ocriplasmin versus 16.0% with placebo (P<0.001) achieved hole closure at Day 28 without vitrectomy. For patients with a baseline macular hole width >250 μm, 5 times more patients treated with ocriplasmin than placebo had successful hole closure without vitrectomy at Day 28 (24.6% versus 4.5%, respectively; P=0.031) in the combined analysis. In both cohorts, successful macular hole closure was maintained through Month 6.

Figure 25. Proportion of Patients with Macular Hole Closure at Day 28 (without Vitrectomy) by Size of Macular Hole at Baseline (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set)[a]



[a]A total of 153 patients had macular hole at baseline; however, macular hole width data were not reported for 1 patient in TG-MV-006.
Note: *P* value from Fisher's exact test for individual studies; *P* value from Cochran-Mantel-Haenszel test for the combined analysis, stratified by study.
Data on file, ThromboGenics.

8.2.4.3 Macular Hole Closure, Irrespective of Vitrectomy

In the Full Analysis Set in TG-MV-006, 84.2% of patients treated with ocriplasmin versus 65.6% with placebo (*P*=0.063, Fisher's exact test), and in TG-MV-007, 65.3% treated with ocriplasmin versus 73.3% with placebo (*P*=0.755) had macular hole closure at Month 6 irrespective of vitrectomy. The similarity of odds ratios between the 2 studies was supported by a non-significant *P* value of the Breslow-Day homogeneity test.

In the combined analysis, a slightly higher proportion of ocriplasmin-treated patients had macular hole closure irrespective of vitrectomy at Month 6, compared with the placebo group:

75.5% versus 68.1% (*P*=0.246 [Cochran-Mantel-Haenszel test]; *P*=0.069 [type 3 analysis from logistic regression]).

The success of macular hole closure with vitrectomy was similar in patients treated with ocriplasmin and placebo.

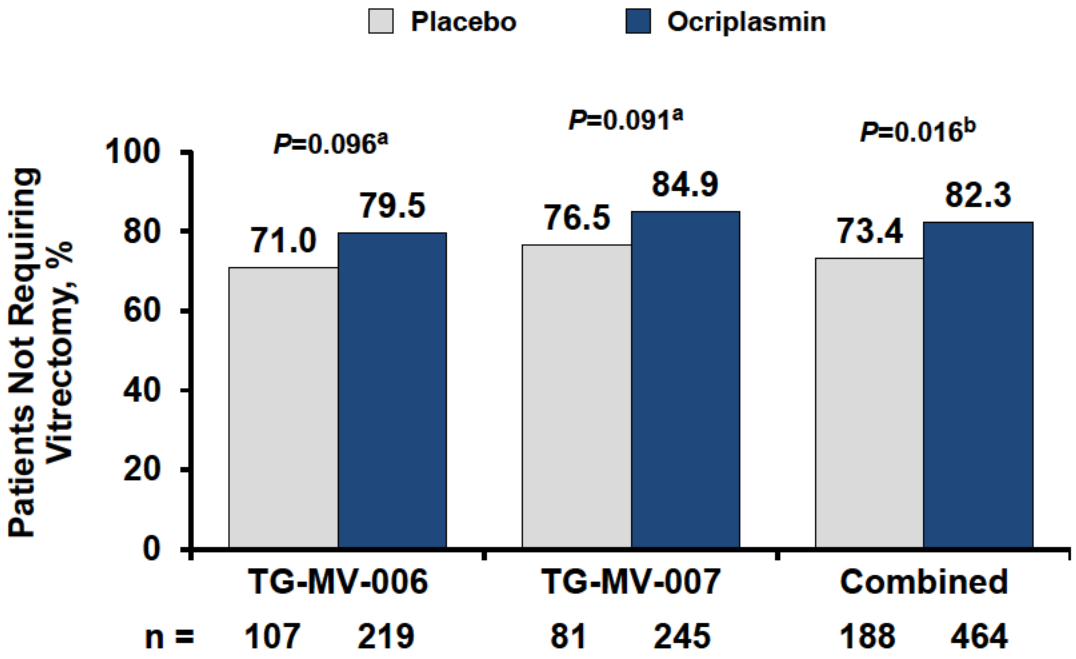
8.2.4.4 Proportion of Patients Not Requiring Vitrectomy

Patients could undergo vitrectomy after Day 28 if deemed necessary by the physician. In addition, patients could have vitrectomy prior to Day 28 if the BCVA in the study eye worsened by ≥2 lines, at the physician's discretion. By Day 28 in the combined (Full) analysis of TG-MV-006 and TG-MV-007, 2 patients in the placebo group (1.1%) and 3 patients in the ocriplasmin group (0.6%) had received a vitrectomy in the study eye.

The proportions of patients who did not require a vitrectomy for the individual studies and the combined analysis, and the time to vitrectomy, are shown Figures 26 and 27. At Month 6, more patients treated with ocriplasmin than placebo did not require a vitrectomy procedure. In the combined analysis at Month 6, 82.3% of patients in the ocriplasmin group and 73.4% in the placebo group had not undergone vitrectomy; the absolute difference at Month 6 was 8.9% (95% CI: 1.7–16.1; *P*=0.016).

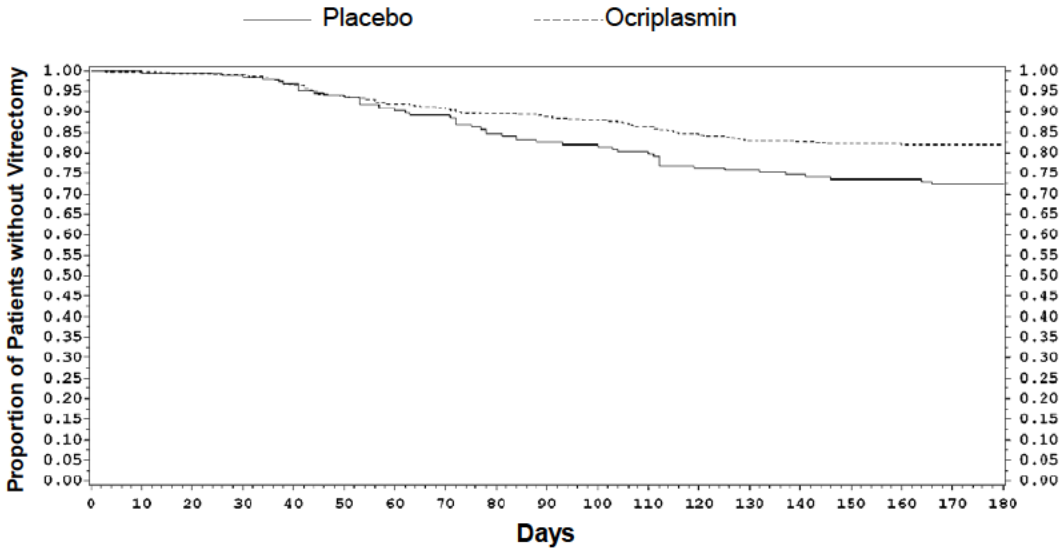
This treatment effect was confirmed using logistic regression analysis. In the model adjusted for baseline covariates, study treatment had a notable effect on the proportion of patients in the combined (Full) analysis set who did not receive a vitrectomy by Month 6 (*P*=0.015, OR: −0.543 [95% CI: 0.889–0.332]).

Figure 26. Proportion of Patients Not Requiring Vitrectomy at Month 6 (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set)



[a]Fisher's exact test; [b]Cochran-Mantel-Haenszel test, stratified by study.
Data on file, ThromboGenics.

Figure 27. Time to Vitrectomy (Combined Analysis: Full Analysis Set)



Data on file, ThromboGenics.

8.2.4.5 Improvement in BCVA

8.2.4.5.1 Mean Change in BCVA

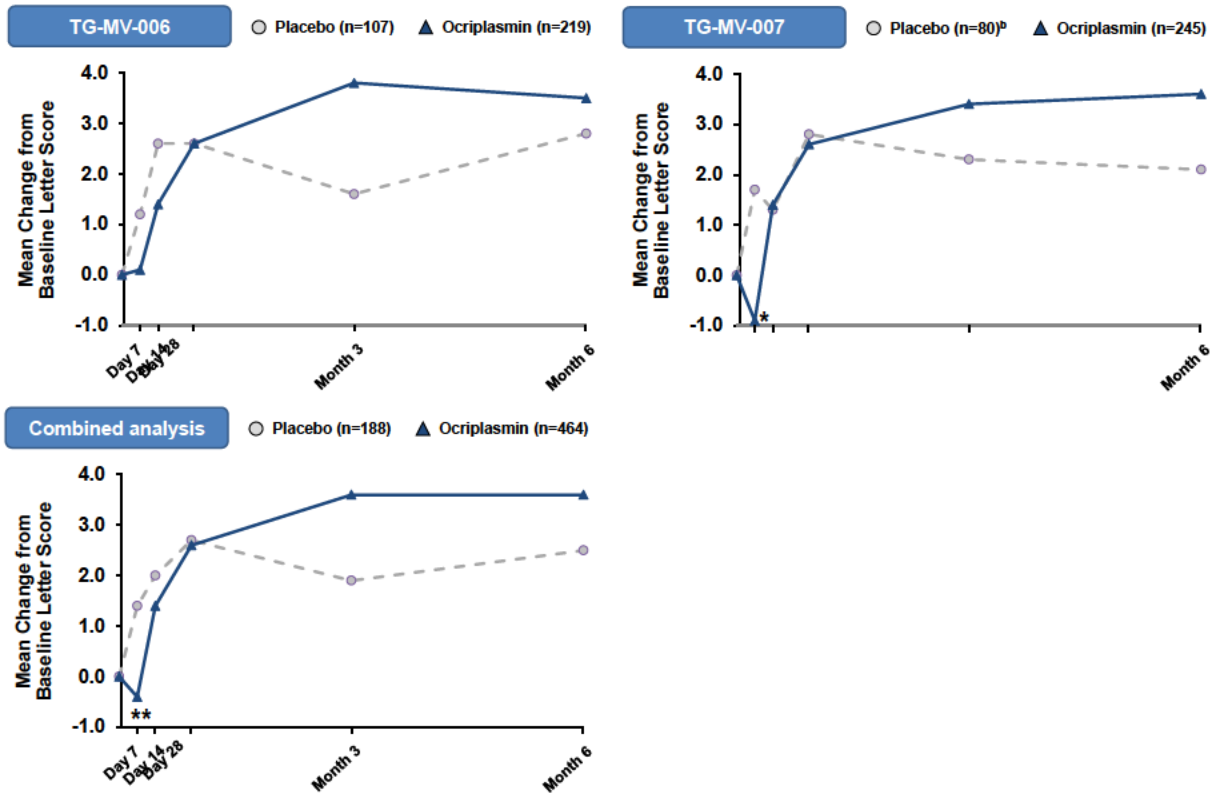
The mean change in visual acuity from baseline over time, irrespective of vitrectomy, is shown in Table 12 and Figure 28. There was a gradual increase from baseline in mean BCVA from Day 14 to Month 6 in the ocriplasmin-treated patients. In contrast, the values were more variable in the placebo-treated patients due to a higher rate of vitrectomy. The results were similar for both TG-MV-006 and TG-MV-007 (Table 12).

Table 12. Change from Baseline in BCVA Letter Score by Study Visit, Irrespective of Vitrectomy (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set)

	TG-MV-006			TG-MV-007			Combined Analysis		
Visit	**Placebo**	**Ocriplasmin 125µg**	***P* value[a]**	**Placebo**	**Ocriplasmin 125µg**	***P* value[a]**	**Placebo**	**Ocriplasmin 125µg**	***P* value[a]**
Baseline	**n=107**	**n=219**		**n=80[b]**	**n=245**		**n=188**	**n=464**	
Mean letter score (SD)	65.3 (9.83)	64.5 (10.86)	—	64.9 (11.58)	63.4 (13.69)	—	65.1 (10.59)	63.9 (12.43)	—
Median letter score	67.0	67.0	—	66.5	67.0	—	67.0	67.0	—
Day 7									
Mean change from BL (SD)	1.2 (5.81)	0.1 (8.12)	0.183	1.7 (5.05)	−0.9 (8.09)	0.008	1.4 (5.49)	−0.4 (8.11)	0.005
Median change from BL	1.0	0.0	—	1.0	0.0	—	1.0	0.0	—
Day 14									
Mean change from BL (SD)	2.6 (5.14)	1.4 (9.60)	0.165	1.3 (5.62)	1.4 (6.82)	0.863	2.0 (5.38)	1.4 (8.24)	0.293
Median change from BL	3.0	2.0	—	1.0	1.0	—	2.0	2.0	—
Day 28									
Mean change from BL (SD)	2.6 (6.50)	2.6 (10.58)	0.950	2.8 (6.13)	2.6 (6.64)	0.823	2.7 (6.33)	2.6 (8.71)	0.861
Median change from BL	2.0	3.0	—	2.0	2.0	—	2.0	2.0	—
Month 3									
Mean change from BL (SD)	1.6 (12.09)	3.8 (10.50)	0.111	2.3 (8.00)	3.4 (7.75)	0.273	1.9 (10.52)	3.6 (9.14)	0.048
Median change from BL	2.0	3.0	—	2.0	3.0	—	2.0	3.0	—
Month 6									
Mean change from BL (SD)	2.8 (9.89)	3.5 (12.30)	0.732	2.1 (9.49)	3.6 (10.35)	0.218	2.5 (9.71)	3.6 (11.30)	0.303
Median change from BL	2.0	3.0	—	2.0	3.0		2.0	3.0	—

Abbreviations: ANOVA, analysis of variance; BCVA, best corrected visual acuity; BL, baseline; SD, standard deviation.
[a]For individual studies, treatment groups were compared with respect to change from baseline using ANOVA model with factors for treatment and baseline visual acuity category (<65 letters, 65–75 letters, >75 letters); for the combined analysis, the model also included a factor for study.
[b]The number of patients in the treatment group is 81; change from baseline was calculated on n = 80.
Data on file, ThromboGenics.

Figure 28. Mean Change in BCVA Over Time (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set)[a]



Abbreviation: BCVA, best corrected visual acuity.
*P=0.008; **P=0.005.
[a]Treatment groups were compared with respect to change from baseline using analysis of variance model with factors for treatment and baseline visual acuity category (< 65 letters, 65–75 letters, >75 letters); for the combined analysis, the model also included a factor for study.
[b]The number of patients in the treatment group is 81; change from baseline was calculated on n = 80.
Data on file, ThromboGenics.

8.2.4.5.2 Categorical Change in BCVA without Vitrectomy

Improved vision without the need for vitrectomy is an important measure of efficacy. Table 13 shows BCVA improvement from baseline in the individual studies and the combined analysis. In the combined analysis, the proportion of patients with a ≥2-line (10 letters) improvement in visual acuity without vitrectomy was approximately 2-fold higher in patients who received ocriplasmin 125 µg compared with placebo (23.7% versus 11.2%, respectively; P<0.001) at 6 months. An even greater difference—nearly 3-fold higher with ocriplasmin than with placebo—was seen for patients showing a ≥3-line (15 letters) improvement in BCVA (9.7% versus 3.7%, respectively; P=0.008) at 6 months without vitrectomy.

Table 13. Categorical Improvement from Baseline in BCVA at Month 6 without Vitrectomy (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set)

Time Point	TG-MV-006				TG-MV-007				Combined Analysis			
	Placebo (n=107) n (%)	Ocriplasmin (n=219) n (%)	Difference (95% CI)[a]	*P* value[b]	Placebo (n=81)[c] n (%)	Ocriplasmin (n=245) n (%)	Difference (95% CI)[a]	*P* value[b]	Placebo (N=188)[d] n (%)	Ocriplasmin (N=464) n (%)	Difference (95% CI)[a]	*P* value[b]
Non-surgical ≥2-line Improvement in BCVA[e]												
Month 6	12 (11.2)	56 (25.6)	14.4 (6.0, 22.7)	0.002	9 (11.1)	54 (22.0)	10.9 (2.3, 19.5)	0.035	21 (11.2)	110 (23.7)	12.5 (6.6, 18.5)	<0.001
Non-surgical ≥3-line Improvement in BCVA[e]												
Month 6	7 (6.5)	23 (10.5)	4.0 (−2.2, 10.2)	0.310	0	22 (9.0)	9.0 (5.4, 12.6)	0.002	7 (3.7)	45 (9.7)	6.0 (2.2, 9.8)	0.008
Non-surgical ≥3-line Improvement from Baseline or Improvement to ≥85 Letters[e]												
Month 6	9 (8.4)	31 (14.2)	5.7 (−1.3, 12.7)	0.154	3 (3.7)	31 (12.7)	8.9 (3.1, 14.8)	0.021	12 (6.4)	62 (13.4)	7.0 (2.3, 11.6)	0.009

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval.
[a]The (absolute) difference and CIs between treatment groups are based on the proportion of successes.
[b]*P* value from Fisher's exact test for individual studies; *P* value from Cochran-Mantel-Haenszel test for the combined analysis, stratified by study.
[c]One patient did not have baseline BCVA measurement; however, this patient had a vitrectomy during the study and therefore did not meet the endpoint based on this criterion; therefore, this patient was included in the denominator for this analysis (81 for the placebo group).
[d]One patient did not have baseline BCVA measurement; however, this patient had a vitrectomy during the study and therefore did not meet the endpoint based on this criterion; therefore, this patient was included in the denominator for this analysis (188 for the placebo group).
[e]For patients who did not have a vitrectomy during the study, non-surgical categorical improvement is defined as values observed at Month 6 or carried forward from previous visits if data are missing; data for patients with an on-study vitrectomy are included up to the date of vitrectomy; patients are considered as failures post-vitrectomy.
Data on file, ThromboGenics.

8.2.4.5.3 Categorical Change in BCVA Irrespective of Vitrectomy

Categorical change in BCVA from baseline at Month 6 irrespective of vitrectomy in the individual studies and the combined analysis is shown on Table 14.

Table 14. Change from Baseline in BCVA at Month 6, Irrespective of Vitrectomy (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set)

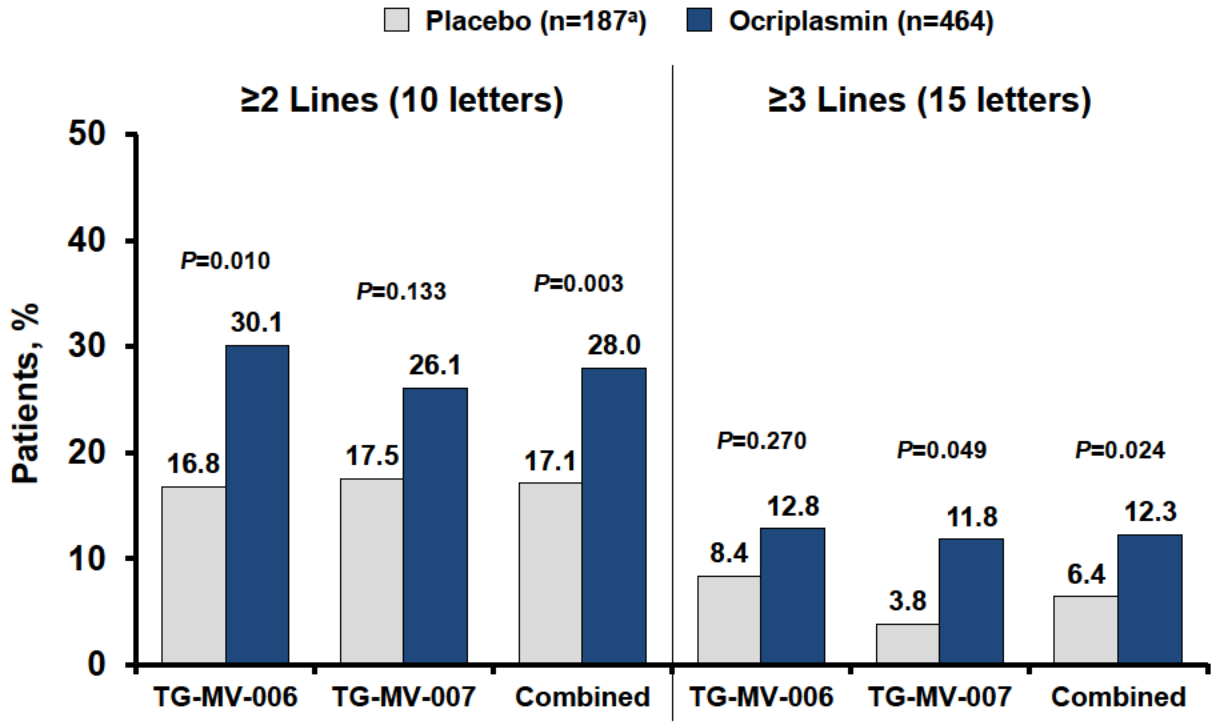
TG-MV-006				TG-MV-007				Combined Analysis			
Placebo (n=107) n (%)	**Ocriplasmin (n=219) n (%)**	**Difference (95% CI)[a]**	***P* value[b]**	**Placebo (n=81)[c] n (%)**	**Ocriplasmin (n=245) n (%)**	**Difference (95% CI)[a]**	***P* value[b]**	**Placebo (n=188)[d] n (%)**	**Ocriplasmin (n=464) n (%)**	**Difference (95% CI)[a]**	***P* value[b]**
≥2-line Improvement											
18 (16.8)	66 (30.1)	13.3 (4.0, 22.7)	0.010	14 (17.5)	64 (26.1)	8.6 (−1.4, 18.6)	0.133	32 (17.1)	130 (28.0)	10.9 (4.1, 17.7)	0.003
≥3-line Improvement											
9 (8.4)	28 (12.8)	4.4 (−2.5, 11.2)	0.270	3 (3.8)	29 (11.8)	8.1 (2.3, 13.9)	0.049	12 (6.4)	57 (12.3)	5.9 (1.3, 10.5)	0.024
≥3-line Improvement from Baseline or Improvement to ≥ 85 Letters											
11 (10.3)	36 (16.4)	6.2 (−1.4, 13.7)	0.179	6 (7.5)	39 (15.9)	8.4 (1.0, 15.8)	0.063	17 (9.1)	75 (16.2)	7.1 (1.8, 12.4)	0.018
≥2-line Worsening											
5 (4.7)	22 (10.0)	5.4 (−0.3, 11.0)	0.133	6 (7.5)	14 (5.7)	−1.8 (−8.2, 4.7)	0.594	11 (5.9)	36 (7.8)	1.9 (−2.3, 6.0)	0.352
≥3-line Worsening											
2 (1.9)	16 (7.3)	5.4 (1.1, 9.7)	0.067	4 (5.0)	10 (4.1)	−0.9 (−6.3, 4.5)	0.753	6 (3.2)	26 (5.6)	2.4 (−0.9, 5.7)	0.180
≥6-line Worsening											
1 (0.9)	3 (1.4)	0.4 (−2.0, 2.8)	>0.999	1 (1.3)	3 (1.2)	−0.0 (−2.8, 2.8)	>0.999	2 (1.1)	6 (1.3)	0.2 (−1.6, 2.0)	0.815

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval.
[a]The (absolute) difference and CIs between treatment groups are based on the proportion of successes.
[b]*P* value from Fisher's exact test for individual studies; *P* value from Cochran-Mantel-Haenszel test for the combined analysis, stratified by study.
[c]One patient did not have baseline BCVA measurement; therefore, the denominator used in this analysis is 80 for placebo group.
[d]One patient did not have baseline BCVA measurement; therefore, the denominator used in this analysis is 187 for placebo group.
Data on file, ThromboGenics.

In the combined (Full) analysis set, a greater percentage of patients treated with ocriplasmin 125 µg showed at least 2 lines of improvement from baseline in BCVA at Month 6, compared with placebo (95% CI: 4.1–17.7, *P*=0.003) (Table 14 and Figure 29). Similar results were reported in the combined analysis for at least 3 lines of improvement in BCVA (95% CI: 1.3–10.5, *P*=0.024).

The treatment effect was confirmed using logistic regression analyses adjusted for baseline covariates (*P*=0.010, OR: 2.726 [95% CI: 1.265–5.874]).

Figure 29. Proportion of Patients Gaining ≥2 Lines and ≥3 Lines in BCVA from Baseline at Month 6 Irrespective of Vitrectomy (TG-MV-006, TG-MV-007, and Combined Analysis: Full Analysis Set)

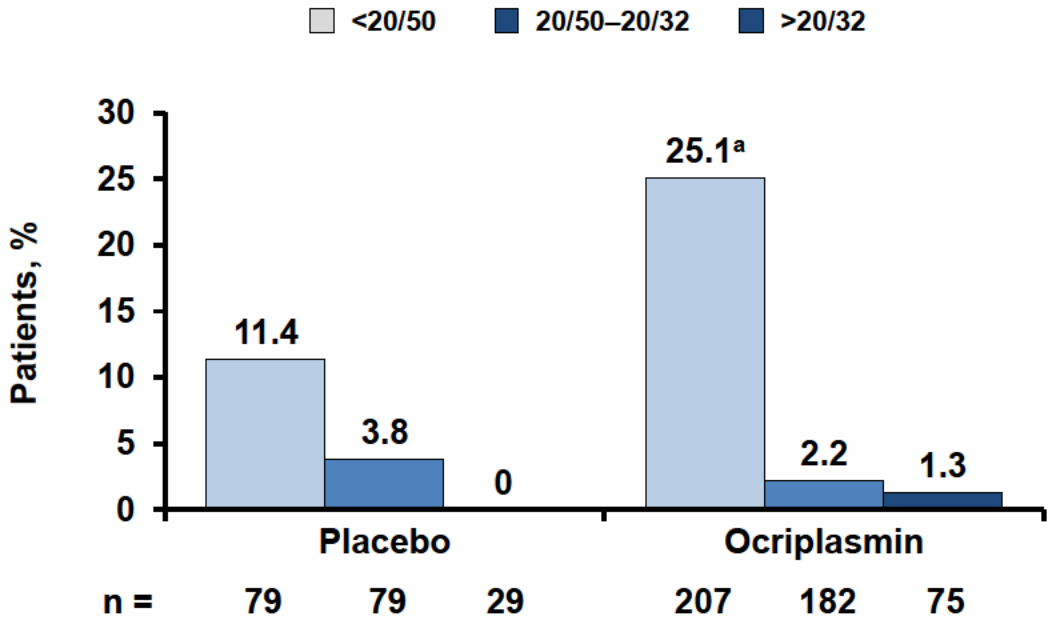


[a]One patient did not have BCVA measurement at baseline; therefore, denominator for placebo group is 187.
Note: *P* value from Fisher's exact test for individual studies; *P* value from Cochran-Mantel-Haenszel test for the combined analysis, stratified by study.
Data on file, ThromboGenics.

Patients with good vision (the mean baseline BCVA for both Phase 3 studies was 64 letters) are unlikely to achieve a ≥3-line gain if visual acuity is already close to 20/20 (85 letters) vision. Therefore, the categorical change in BCVA of ≥3 lines is also presented with the addition of patients whose vision improved by ≥85 letters. This "ceiling effect" is highlighted in Figure 30,

which illustrates the magnitude of the ≥3-line gain in the subset of patients whose baseline vision would permit BCVA improvement of up to 5 lines.

Figure 30. Proportion of Patients Gaining ≥3 Lines (15 Letters) in BCVA at Month 6 by Visual Acuity at Baseline Irrespective of Vitrectomy (Combined Analysis: Full Analysis Set)



[a]*P*<0.010 versus placebo; Cochran-Mantel-Haenszel test, stratified by study.

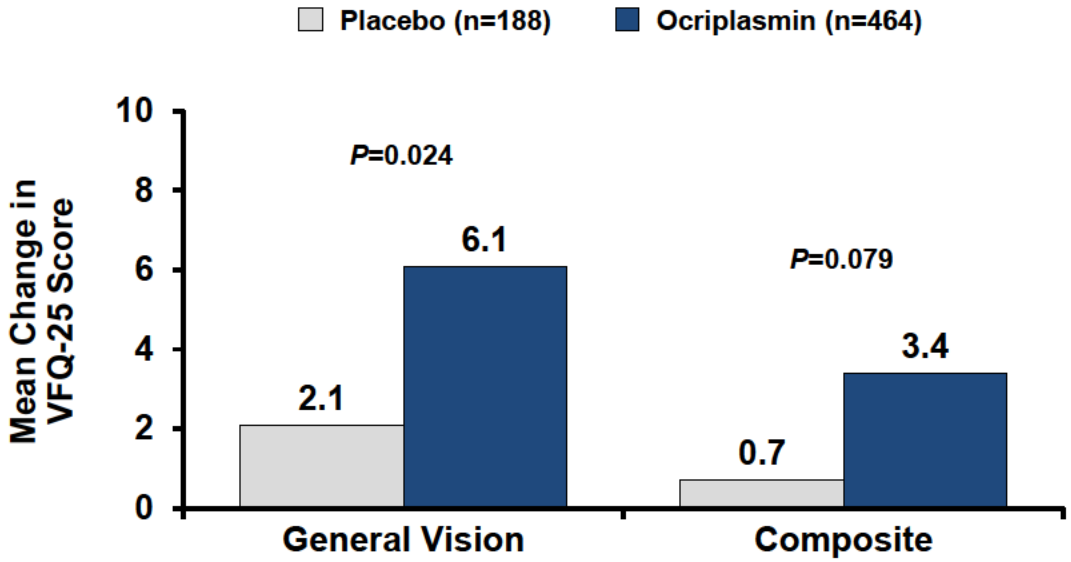
The proportion of patients who showed worsening of BCVA by at least 2 lines was comparable between treatment groups at Month 6 (Table 14). No more than 6% of patients in each treatment group had a ≥3-line or ≥6-line worsening in BCVA at Month 6.

8.2.4.6 Improvement in Visual Function: VFQ-25

Mean improvements in VFQ-25 scores with ocriplasmin compared with placebo were observed in both of the Phase 3 studies. In TG-MV-006, mean improvements in the subscale and composite scores were generally greater in patients treated with ocriplasmin, although no treatment differences were observed at Month 6 by ANOVA analysis. In TG-MV-007, mean improvements in each subscale score and the composite score were observed in patients treated with ocriplasmin, whereas slight worsening was observed for 6 of the 12 subscale scores and the composite score with placebo. A difference in favor of ocriplasmin was observed for improvement in the general health subscale score (2.2 with ocriplasmin, −2.4 with placebo; *P*=0.038) at Month 6 in TG-MV-007.

In the combined analysis, mean increases from baseline at Month 6 were observed in the placebo group for 7 of the 12 VFQ-25 subscale scores and in the composite score; mean increases were observed in the ocriplasmin group for all of the subscale scores and in the composite score. The improvements were numerically greater with ocriplasmin, compared with placebo, in each subscale score and in the composite score. A difference in favor of ocriplasmin was observed for the improvement in the general vision subscale score (*P*=0.024) and the composite score (*P*=0.079) (Figure 31).

Figure 31. Visual Function: Change from Baseline in VFQ-25 General Vision and Composite Scores at Month 6 (Combined Analysis: Full Analysis Set)



Abbreviation: VFQ-25, National Eye Institute 25-item Visual Functioning Questionnaire.
Note: Treatment groups are compared for change from baseline using analysis of variance model with factors for treatment, baseline VFQ-25 score, and study.
Data on file, ThromboGenics.

8.2.5 Responder Analyses

8.2.5.1 Association of VMA Resolution and Improvement in BCVA

In the combined analysis, patients who achieved VMA resolution at Day 28 were more likely to have improvements in BCVA, compared with patients without VMA resolution. In the ocriplasmin group, 44.7% of patients who achieved the primary endpoint gained ≥2 lines (21.2% in the placebo group) and 20.3% of patients gained ≥3 lines (15.8% with placebo) of BCVA at Month 6 (Table 15).

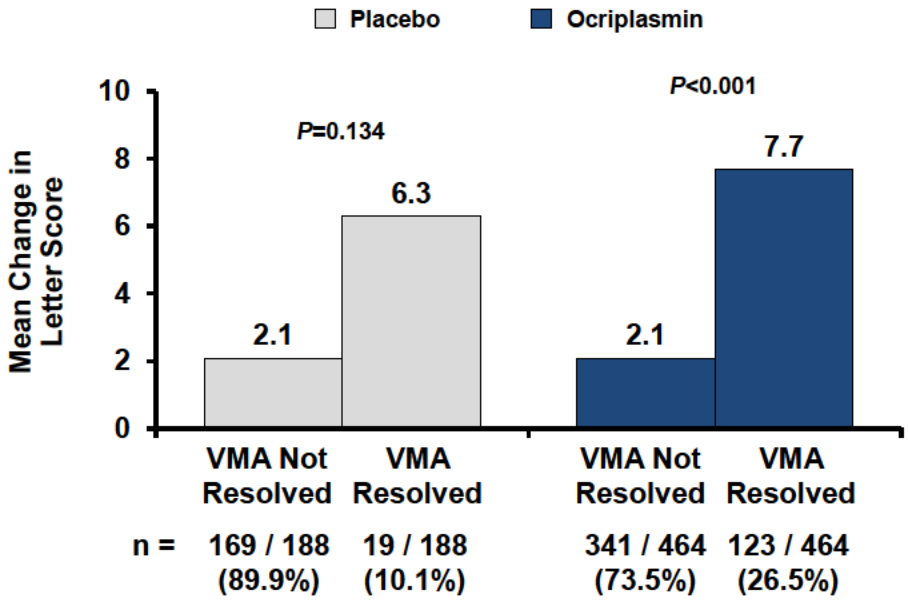
Table 15. Categorical Improvement from Baseline in BCVA at Month 6 by Outcome of the Primary Efficacy Endpoint, Irrespective of Vitrectomy (Combined Analysis: Full Analysis Set)

Treatment Group	Success on Efficacy		Failure on Efficacy		Difference (95% CI)[a]	Effect of Efficacy Endpoint	
	N	n (%)	N	n (%)		*P* value[b]	Odds Ratio (95% Wald CI)
≥2-line Improvement							
Ocriplasmin	123	55 (44.7)	341	75 (22.0)	−22.7 (−32.5, −12.9)	0.006	2.079 (1.232, 3.509)
Placebo	19	4 (21.1)	169[c]	28 (16.7)	−4.4 (−23.6, 14.8)		
≥3-line Improvement							
Ocriplasmin	123	25 (20.3)	341	32 (9.4)	−10.9 (−18.7, −3.2)	0.077	1.813 (0.937, 3.507)
Placebo	19	3 (15.8)	169[c]	9 (5.4)	−10.4 (−27.2, 6.3)		
≥3-line Improvement from Baseline or Improvement to ≥85 Letters							
Ocriplasmin	123	34 (27.6)	341	41 (12.0)	−15.6 (−24.2, −7.0)	0.005	2.345 (1.293, 4.254)
Placebo	19	4 (21.1)	169[c]	13 (7.7)	−13.3 (−32.1, 5.5)		

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval.
[a]The (absolute) difference between treatment groups and CIs are based on the proportion of successes.
[b]*P* value is from type 3 analysis of effects from multivariate logistic regression.
[c]One patient did not have baseline BCVA measurement; therefore, the denominator used in this analysis is 168 for placebo group.
Data on file, ThromboGenics.

At baseline, the mean BCVA was 61.7 letters (20/63) in ocriplasmin-treated patients who achieved VMA resolution at Day 28. The mean improvement in BCVA from baseline at Month 6 in the ocriplasmin group was 7.7 letters among patients who achieved VMA resolution and 2.1 letters among those who did not; the corresponding values in the placebo group were 6.3 and 2.1 letters, respectively. The mean improvement in BCVA from baseline at Month 6 in patients who achieved VMA resolution was similar in the ocriplasmin and placebo groups. However, the improvement occurred in only 10.1% of patients in the placebo group versus 26.5% of patients in the ocriplasmin group (Figure 32).

Figure 32. Improvement in Mean BCVA at Month 6 by Resolution of VMA at Day 28 (Combined Analysis: Full Analysis Set)

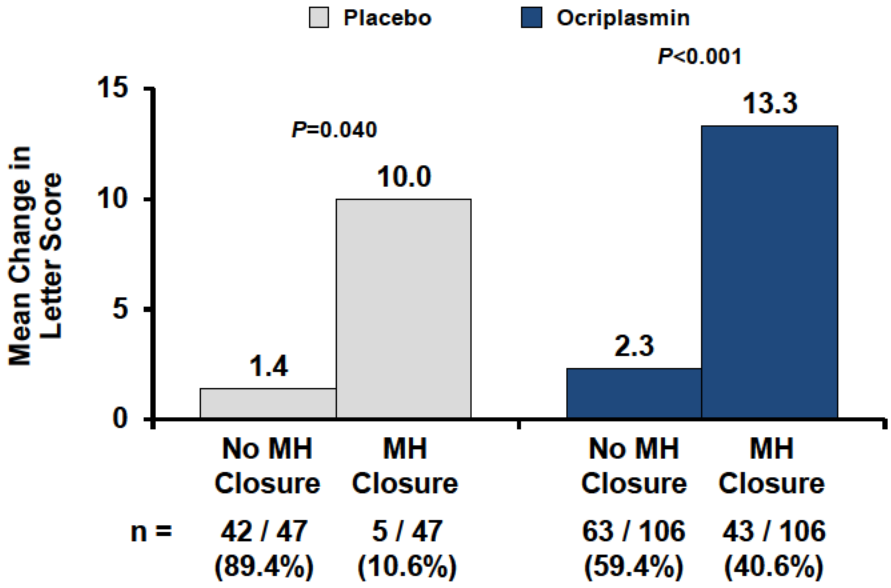


Abbreviations: BCVA, best corrected visual acuity; VMA, vitreomacular adhesion.
Note: For individual studies, treatment groups are compared with respect to the change from baseline using analysis of variance model with factors for treatment and baseline visual acuity category (<65, 65-75, >75); for combined analysis, the model also includes a factor for study.
Data on file, ThromboGenics.

8.2.5.2 Association of Macular Hole Closure and Improvement in BCVA

In the combined analysis, patients with pharmacologic macular hole closure at Day 28 (without vitrectomy) were more likely to have improvement in BCVA, compared to patients without macular hole closure. In the ocriplasmin group, the mean improvement from baseline (baseline BCVA was 57.7 letters, 20/80) at Month 6 was 13.3 letters among patients with, and 2.3 letters among those without, pharmacologic macular hole closure at Day 28; the corresponding values in the placebo group were 10.0 and 1.4 letters, respectively (Figure 33).

Figure 33. Improvement in Mean BCVA at Month 6 by Macular Hole Closure at Day 28 (Combined Analysis: Full Analysis Set)



Abbreviations: MS, macular hole; VMA, vitreomacular adhesion.
Note: For individual studies, treatment groups are compared with respect to the change from baseline using analysis of variance model with factors for treatment and baseline visual acuity category (<65, 65-75, >75); for combined analysis, the model also includes a factor for study.
Data on file, ThromboGenics.

Among ocriplasmin-treated patients with pharmacologic macular hole closure at Day 28, the proportion gaining ≥2 lines or ≥3 lines of visual acuity increased over the time of the studies. At Month 6, the majority (72.1%) of ocriplasmin-treated patients had a ≥2-line improvement and half (48.8%) had a ≥3-line improvement in BCVA (Table 16). In addition, 51.2% of ocriplasmin-treated patients who achieved closure of a macular hole had an improvement from baseline of ≥3 lines in BCVA or to ≥85 letters at Month 6.

Table 16. Proportion of Patients with BCVA Improvement of ≥2 or ≥3 Lines at Month 6 Among Those with Macular Hole Closure at Day 28 without Vitrectomy (Combined Analysis: Full Analysis Set)

	Placebo (n=5), n (%)	Ocriplasmin (n=43), n (%)	Difference (95% CI)[a]	*P* value[b]	Exact Odds Ratio (95% CI)[c]
≥2-line (10 Letters) Improvement	2 (40.0)	31 (72.1)	32.1 (−12.9, 77.1)	0.145	3.783 (0.382, 51.064)
≥3-line (15 Letters) Improvement	2 (40.0)	21 (48.8)	8.8 (−36.6, 54.3)	0.824	1.237 (0.125, 16.390)

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval.
[a]The difference and CIs between treatment groups are based on the percentage of successes.
[b]*P* value from Cochran-Mantel-Haenszel test for the combined analysis, stratified by study.
[c]For individual studies, exact odds ratio and confidence interval are obtained from logistic regression with a factor for randomized treatment; for the combined analysis, the model includes randomized treatment and study.
Data on file, ThromboGenics.

8.2.5.3 Association of VMA Resolution and Improvement in VFQ-25 Score

In the combined analysis, among patients in the ocriplasmin group who achieved VMA resolution at Day 28, mean improvement in the general vision subscale score from baseline at Month 6 was 8.4, compared with 5.3 among those who failed the endpoint; and mean improvement in the composite score was 5.7 compared with 2.6, respectively. In the placebo group, the mean change in the general vision subscale score at Month 6 was 11.3 versus 1.1 in patients with, versus without, VMA resolution at Day 28; and mean change in the composite score was −0.2 versus 0.7, respectively.

Based on the ANOVA model, outcome of the primary efficacy endpoint had a significant effect on improvement in the general vision subscale score (P=0.012) and the composite score (P=0.015).

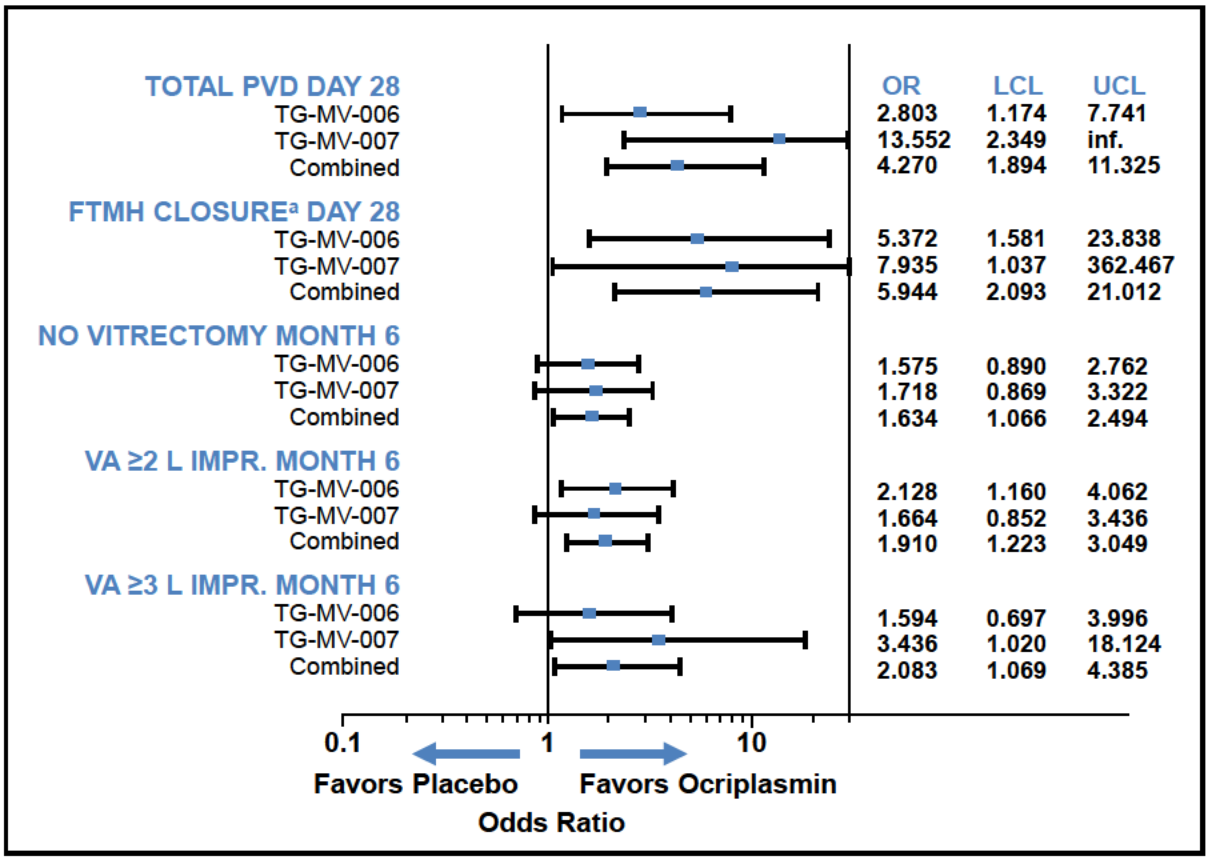
8.2.5.4 Association of Macular Hole Closure and Improvement in VFQ-25 Score

In the combined analysis, among patients in the ocriplasmin group who achieved pharmacologic closure of a macular hole, mean improvement from baseline in the general vision subscale score at Month 6 was 16.0, compared with 4.7 among those who failed the endpoint; and mean improvement in the composite score was 9.0 compared with 1.4, respectively. In the placebo group, the mean change in the general vision subscale score at Month 6 was 2.5 versus 1.8 in patients with, versus without, pharmacologic macular hole closure; and mean change in the composite score was −1.1 versus −1.2, respectively.

8.2.6 Secondary Endpoints Analysis

Analysis of all secondary endpoints confirmed the benefit of ocriplasmin relative to placebo for each Phase 3 study and in the combined analysis (Figure 34). The treatment effect was significant in all analyses for the secondary endpoint, total PVD at Day 28, and for other secondary endpoints including pharmacologic macular hole closure; no vitrectomy; and ≥2- line and ≥3-line improvement in BCVA, irrespective of whether vitrectomy was performed.

Figure 34. Odds Ratios (with 95% CIs) of the Comparison of Ocriplasmin versus Placebo for Secondary Endpoints (Full Analysis Set)



Abbreviations: CI, confidence interval; FTMH, full thickness macular hole; IMPR., improvement; L, line; LCL, lower confidence limit; OR, odds ratio; PVD, posterior vitreous detachment; UCL, upper confidence limit; VA, visual acuity.
[a]Without vitrectomy.
Data on file, ThromboGenics.

8.2.7 Efficacy Conclusions

The efficacy of ocriplasmin for the treatment of symptomatic VMA including macular hole was demonstrated in 2 separate placebo-controlled studies, with the primary and secondary efficacy parameters showing positive results. The onset of effect was rapid and was sustained for the duration of the studies. In the combined analysis of TG-MV-006 and TG-MV-007, ocriplasmin achieved the primary efficacy endpoint, VMA resolution at Day 28, in 26.5% of patients, compared with 10.1% in the placebo group. The actual difference observed in the studies may underestimate the real difference between ocriplasmin and no treatment (the more clinically relevant situation for these patients). It has been hypothesized that intravitreal injections

themselves have the potential to exert at least some effect on VMA by a hydrodynamic mechanism. Subgroup analyses confirmed the efficacy of ocriplasmin for the primary endpoint across all subgroups defined by various demographic and ocular characteristics at baseline, including age, and BCVA, ERM, macular hole, lens, and DR status, and the physician's opinion of the likelihood of the patient requiring vitrectomy.

Results of the secondary endpoints provided additional evidence of the efficacy of ocriplasmin. Ocriplasmin treatment led to significantly higher rates of total PVD induction at Day 28. Among patients with a macular hole at baseline, more treated with ocriplasmin (40.6%) than placebo (10.6%) had hole closure at Day 28, by combined analysis. Fewer ocriplasmin- than placebo-treated patients required vitrectomy by Month 6. Improvement in BCVA from baseline, irrespective of whether vitrectomy was required, was greater with ocriplasmin than placebo. Changes in VFQ-25 scores also favored ocriplasmin treatment. Analysis of secondary endpoints confirmed the consistency of ocriplasmin treatment effect across the individual studies and in the combined analysis.

Successful resolution of VMA and closure of macular holes were strongly associated with improvements in functional measures such as BCVA and VFQ-25 scores. In the ocriplasmin group at Month 6, 45% of those who achieved VMA resolution at Day 28 had a ≥2-line improvement and 20% had a ≥3-line improvement in BCVA on combined analysis. In ocriplasmin-treated patients with pharmacologic macular hole closure at Day 28, 72% had a ≥2-line improvement and 49% had a ≥3-line improvement in BCVA at Month 6 on combined analysis.

The studies showed statistically significant and clinically meaningful efficacy for ocriplasmin. Ocriplasmin demonstrated the ability to resolve the underlying pathology of VMA, thereby potentially reducing disease progression and complications in those patients. The onset of action was rapid and the benefit sustained over the 6-month follow-up period. The results were robust and consistent across endpoints, analyses, subgroups, and studies.

9 SAFETY

Ocriplasmin has an acceptable safety profile for the treatment of symptomatic VMA, based on safety data from clinical studies with follow-up of up to 1 year. The limited systemic exposure and the rapid inactivation provide for reduced drug exposure and minimal risks of treatment.

9.1 Methods

9.1.1 Safety Evaluation Plan

The safety profile of ocriplasmin was based on the results from 7 completed clinical studies (Table 17). Safety evaluations were performed using the Safety Set, which allocated patients to treatment groups based on the treatment actually received.

The 7 completed studies included in the Safety Set are as follows:

- 2 Phase 3, randomized, placebo-controlled Phase 3 studies: TG-MV-006 and TG-MV-007
- 3 controlled Phase 2 studies: TG-MV-002, TG-MV-003, TG-MV-004
- 2 uncontrolled Phase 2 studies: TG-MV-001, TG-MV-010

Safety findings from ongoing studies that were relevant to the safety profile of ocriplasmin are also included. The ongoing studies at the time of the data cut-off are as follows:

- 1 controlled Phase 2 study in wet AMD: TG-MV-005
- 1 controlled Phase 2 pediatric vitrectomy study: TG-MV-009
- 1 controlled Phase 3b study in patients with symptomatic VMA: TG-MV-014
- 1 open-label Phase 2 study in patients with VMT including macular hole: TG-MV-008
- 1 open-label Phase 2 study in patients with VMA associated with neovascular AMD: JSEI-TG-AMD-001

Table 17. Number of Patients Treated in Completed Studies by Treatment Received (Safety Set)

Study	Ocriplasmin						Placebo	Sham	No Treatment
	25 µg	50 µg	75 µg	125 µg	175 µg	Any Dose			
TG-MV-001	30	10	11	9	0	60	0	0	0
TG-MV-003	29	0	33	32	0	94	31	0	0
TG-MV-010	0	0	0	34	0	34	0	0	4
Subtotal[a]	**59**	**10**	**44**	**75**	**0**	**188**	**31**	**0**	**4**
TG-MV-002	8	0	15	15	0	38	0	13	0
TG-MV-004	0	0	12	27	11	50	0	12	0
TG-MV-006	0	0	0	220[c]	0	220	106	0	0
TG-MV-007	0	0	0	245	0	245	81	0	0
Subtotal[b]	**8**	**0**	**27**	**507**	**11**	**553**	**187**	**25**	**0**
Total	**67**	**10**	**71**	**582**	**11**	**741**	**218**	**25**	**4**

[a]Subtotal for pre-planned vitrectomy studies.
[b]Subtotal for studies without pre-planned vitrectomy.
[c]One patient in TG-MV-006 randomized to placebo was inadvertently treated with ocriplasmin, and is included in the ocriplasmin group for the Safety Set.
Data on file, ThromboGenics.

Safety results are generally presented for 2 groups of patients. The first group includes patients in the Phase 3, randomized, placebo-controlled studies, as these data allow for comparisons between ocriplasmin and placebo in patients without preplanned vitrectomy, thereby minimizing the confounding influence of the surgical procedure. The second group includes patients in all 7 completed, controlled and uncontrolled studies, including those with preplanned vitrectomy. For notable and clinically relevant adverse events (AEs), patients from ongoing studies were included.

The assessments of intensity and relationship to study treatment are those of the investigator unless otherwise noted. Only AEs that occurred from the time of injection to and including the last study visit were considered to be treatment-emergent AEs (TEAEs).

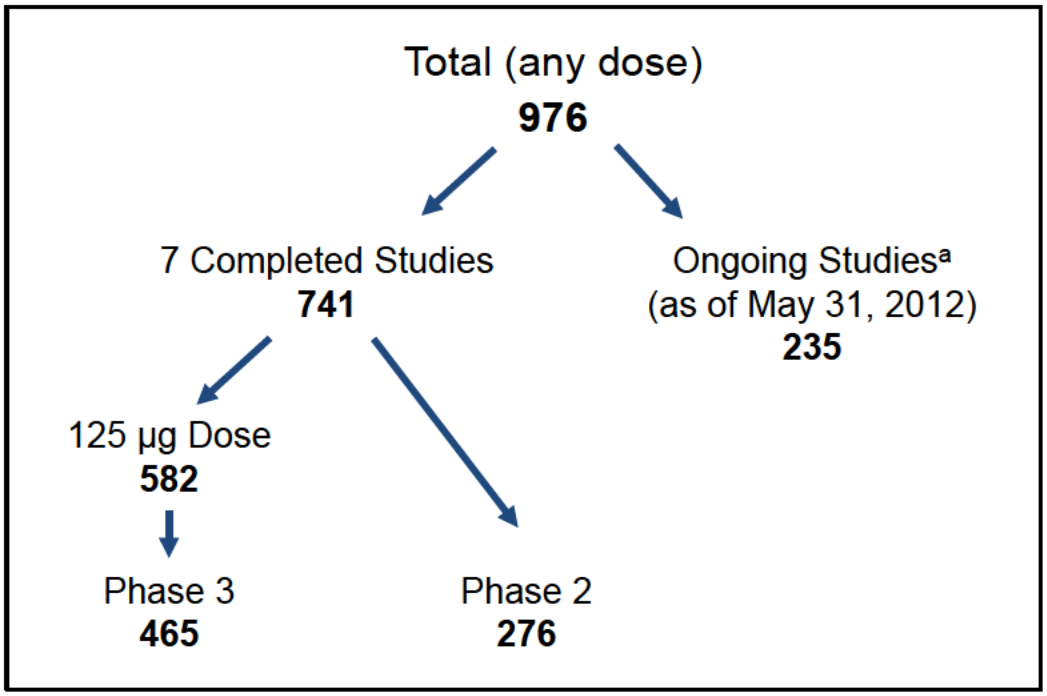
9.2 Extent of Exposure

A total of 976 patients received any dose of ocriplasmin (Figure 35) in completed and ongoing studies as of May 31, 2012. Of these patients, 741 from the 7 completed studies received

ocriplasmin intravitreally, with 582 having received the recommended 125 µg dose. A total of 465 patients received ocriplasmin 125 µg in the Phase 3, randomized, placebo-controlled studies. All except 12 patients have received a single intravitreal injection of ocriplasmin: 3 patients received ocriplasmin in the fellow eye (these patients participated in more than 1 study), and 9 patients in TG-MV-004 received 2 (n = 2) or 3 (n = 7) doses of ocriplasmin in the same eye at monthly intervals (in studies that allowed additional doses in nonresponders).

From the time of the database cut-off date for the 7 completed studies, an additional 235 patients have received ocriplasmin in ongoing clinical studies.

Figure 35. Exposure to Intravitreal Ocriplasmin



[a]Ongoing studies include ongoing studies, patients in follow-up, or final study report is being prepared.
Data on file, ThromboGenics.

In addition to those who received intravitreal ocriplasmin, 97 subjects/patients received the drug via intravenous administration in doses ranging from 0.1 to 5 mg /kg in 5 studies of ocriplasmin for the treatment of vascular conditions. These studies were discontinued for commercial reasons and not for any safety concerns. The limited safety data from these studies are presented in the BLA but not in this briefing document. The reasons for not focusing on these safety data are the

substantial differences regarding indications, route of administration, and doses in the intravenous studies versus the intravitreal studies.

9.2.1 Patient Disposition

Patient disposition was balanced between treatment groups in the Safety Set, with more than 90% of patients completing the studies (Table 18). Per the single administration of the study treatment at the start of the clinical trial, patients who withdrew had already received the entire intended study treatment and have been included in the safety population. No meaningful difference in the rates of discontinuation for AEs or other reasons was reported. Deaths leading to study discontinuation occurred in 5 of 741 patients treated with ocriplasmin and 2 of 247 patients in the control groups (0.7% and 0.8%, respectively) in all studies combined; all deaths were due to systemic events and not considered drug-related.

Table 18. Patient Disposition in Phase 3, Randomized, Placebo-Controlled Studies and All Completed Studies (Safety Set)

	Phase 3, Randomized, Placebo-Controlled Studies		All Completed Studies	
	Placebo	Ocriplasmin 125 µg	Control[a]	Ocriplasmin, Any Dose
	n (%)	n (%)	n (%)	n (%)
Safety set	187 (100.0)	465[b] (100.0)	247 (100.0)	741 (100.0)
Completed study	171 (91.4)	436 (93.8)	228 (92.3)	701 (94.6)
Discontinued from study	16 (8.6)	29 (6.2)	19 (7.7)	40 (5.4)
Reasons for discontinuation				
Adverse event	2 (1.1)	4 (0.9)[c]	2 (0.8)[c]	7 (0.9)[d]
Investigator decision	1 (0.5)	0	1 (0.4)	0
Withdrew consent	8 (4.3)	13 (2.8)	9 (3.6)	17 (2.3)
Lost to follow-up	5 (2.7)	8 (1.7)	5 (2.0)	10 (1.3)
Death[e]	0	4 (0.9)	2 (0.8)	5 (0.7)
Other	0	0	0	1 (0.1)

[a]Patients allocated to placebo, sham injection, or no treatment.
[b]One patient who was randomized to receive placebo inadvertently received ocriplasmin. For the safety analysis, this patient was counted in the ocriplasmin group.
[c]One patient discontinued the study due to an AE (metastatic brain cancer, unrelated to ocriplasmin) and subsequently died due to this condition more than 30 days after study discontinuation and is therefore counted in this table in the "adverse event" row rather than the "death" row.
[d]Reasons for discontinuation were reported as "other" for 1 patient and as "investigator decision" for 1 patient. A review of these cases resulted in changing the reason for discontinuation for these 2 patients to "adverse event"; each patient is counted only in the "adverse event" row.
[e]Deaths were due to non-ocular adverse events and were considered unrelated to study drug.
Data on file, ThromboGenics.

At baseline in the Phase 3, randomized, placebo-controlled studies, the most common ocular conditions in the study eye in the ocriplasmin 125 µg group were vitreous adhesions (99.4% of patients), cataract (61.1%), maculopathy (35.9%), prior cataract surgery (33.5%), and macular holes (32.5%). More patients in the ocriplasmin than in the placebo group had a history of cataract surgery (33.5% versus 24.6%), consistent with the greater number of pseudophakic patients in the ocriplasmin group at baseline (see Table 9). The incidences of histories of other ocular conditions, including macular degeneration, macular edema, nuclear cataract, and vitreous detachment, were similar (≤5% difference) between treatment groups. The ocular conditions at

baseline for all studies combined are consistent with the results for the Phase 3, randomized, placebo-controlled studies.

There were no clinically important differences between the ocriplasmin and placebo groups, or between the Phase 3, randomized, placebo-controlled studies and the all studies combined group, in the percentage of patients taking study eye and non-ocular medications.

9.3 Deaths

A total of 8 deaths occurred during the clinical development program, including 2 of 247 (0.8%) control patients, both of whom had received sham injection; and 6 of 741 (0.8%) ocriplasmin-treated patients, who had received 75 µg (n = 1) or 125 µg (n = 5) doses. One patient had an AE of metastatic brain cancer and discontinued the study. The patient died more than 30 days after study discontinuation; the reason for study discontinuation is recorded as an adverse event in Table 18 (Patient Disposition), and in Table 19 is counted both in "AEs leading to withdrawal" and in "AEs with fatal outcome." All patients died of causes unrelated to ocular AEs and all deaths were determined to be unrelated to the study drug. Brief narratives for these patients are provided in Appendix C.

9.4 Overview of Adverse Events

Ocriplasmin was generally well tolerated. No evidence of systemic effects was observed, which is consistent with the route of administration and mechanism of action of ocriplasmin, a rapidly inactivated agent that is cleared from the circulation with a half-life of several hours.

In the Phase 3, randomized, placebo-controlled studies, the proportion of patients with at least 1 AE was 76.6% in the ocriplasmin group and 69.0% in the placebo group, and the proportion with drug-related AEs was 40.0% and 21.4%, respectively (Table 19). Most of the AEs were mild or moderate in severity. Similar rates of severe AEs were observed in the ocriplasmin and placebo groups (8.4% and 7.5%, respectively). The rate of Serious AEs (~13%), drug-related Serious AEs (3.2% in both groups), and AEs leading to study withdrawal (~1%) were also similar in the ocriplasmin and placebo groups.

Table 19. Overview of All Adverse Events in Phase 3, Randomized, Placebo-Controlled Studies and All Completed Studies (Safety Set)

	Phase 3, Randomized, Placebo-Controlled Studies		All Completed Studies	
Patients, n (%)	**Placebo n=187**	**Ocriplasmin 125 µg n=465**	**Control[a] n=247**	**Ocriplasmin Any Dose n=741**
≥1 AE	129 (69.0)	356 (76.6)	180 (72.9)	593 (80.0)
Related AE	40 (21.4)	186 (40.0)	50 (20.2)	263 (35.5)
Severe AE	14 (7.5)	39 (8.4)	23 (9.3)	62 (8.4)
Serious AE	24 (12.8)	62 (13.3)	34 (13.8)	100 (13.5)
Related Serious AE	6 (3.2)	15 (3.2)	6 (2.4)	16 (2.2)
AE leading to withdrawal[b]	2 (1.1)	4 (0.9)	2 (0.8)	7[c] (0.9)
AE with fatal outcome[d]	0	5[b] (1.1)	2 (0.8)	6[b] (0.8)

Abbreviation: AE, adverse event.
[a]Patients allocated to placebo, sham injection, or no treatment.
[b]One patient discontinued from the study due to metastatic brain cancer (unrelated to ocriplasmin) and subsequently died due to this condition more than 30 days after study discontinuation; in this table, the patient is counted in 2 rows: “AE leading to withdrawal” and “AE with fatal outcome.”
[c]Reasons for discontinuation were reported as "other" for 1 patient (ocriplasmin 25 µg) and as "investigator decision" for 1 patient (ocriplasmin 50 µg); a review of these cases resulted in changing the reason for discontinuation for these 2 patients to “adverse event"; each patient is counted in the “AE leading to withdrawal” row.
[d]All AEs with fatal outcome were non-ocular AEs and were considered unrelated to study drug.
Data on file, ThromboGenics.

9.4.1 Non-Ocular Adverse Events

The most common non-ocular events reported by at least 2% of patients in the Safety Set were nausea, bronchitis, and headache. With the exception of nausea, the rate of each of these AEs was similar with ocriplasmin 125 µg and placebo (Table 20).

Table 20. Non-Ocular Adverse Events Reported for >2% of Patients in Phase 3, Randomized, Placebo-Controlled Studies and All Completed Studies (Safety Set)

System Organ Class Preferred Term Category	Phase 3, Randomized, Placebo-Controlled Studies		All Completed Studies	
	Placebo n=187	Ocriplasmin 125 µg n=465	Control[a] n=247	Ocriplasmin Any Dose n=741
Any non-ocular event, n (%)	53 (28.3)	140 (30.1)	82 (33.2)	255 (34.4)
Bronchitis	3 (1.6)	13 (2.8)	5 (2.0)	16 (2.2)
Headache	4 (2.1)	12 (2.6)	11 (4.5)	32 (4.3)
Nausea	1 (0.5)	12 (2.6)	3 (1.2)	22 (3.0)

[a]Patients allocated to placebo, sham-injection, or no treatment.
Data on file, ThromboGenics.

9.4.2 Ocular Adverse Events

In the randomized, placebo-controlled studies, the proportion of patients with at least 1 study-eye ocular event was higher with ocriplasmin than placebo (Table 21). These events were mild to moderate in intensity and consistent with the mode of action of ocriplasmin. A lower rate of Serious AEs and/or AEs that were considered as severe in intensity was noted in the ocriplasmin group, compared with the placebo group.

Table 21. Ocular Adverse Events in Study Eye by Intensity in Phase 3, Randomized, Placebo-Controlled Studies and All Completed Studies (Safety Set)

System Organ Class Preferred Term Category	Phase 3, Randomized, Placebo-Controlled Studies		All Completed Studies	
	Placebo n=187	Ocriplasmin 125µg n=465	Control[a] n=247	Ocriplasmin Any Dose n=741
AEs in Study Eye, n (%)				
Any ocular AE	99 (52.9)	317 (68.2)	141 (57.1)	529 (71.4)
Any ocular Serious AE	20 (10.7)	36 (7.7)	22 (8.9)	57 (7.7)
Any ocular severe AE	11 (5.9)	23 (4.9)	13 (5.3)	33 (4.5)

Abbreviation: AE, adverse event.
[a]Patients allocated to placebo, sham-injection, or no treatment.
Data on file, ThromboGenics.

Table 22 shows the study eye AEs reported by at least 2% of ocriplasmin-treated patients in the randomized, placebo-controlled studies and for all studies combined. Adverse events that were considered suspected adverse drug reactions (ADRs) as judged by the Sponsor and occurring in the study eye, ie, there was a reasonable possibility that these events were treatment-related, are shown in Table 23.

The majority of AEs that occurred more frequently in the Phase 3, randomized, placebo-controlled studies in ocriplasmin-treated patients were consistent with the intended vitreolytic effects of the drug. These included vitreous floaters (16.8% versus 7.5% for ocriplasmin and placebo, respectively), photopsia (11.8% versus 2.7%), eye pain (13.1% versus 5.9%), and blurred vision (8.4% versus 3.2%). AEs observed with a higher frequency in the placebo-treated patients were macular holes, increased IOP, and cataract. The lower incidence of cataract in ocriplasmin-treated patients is consistent with the lower rate of vitrectomy in that group. Fewer ocriplasmin than placebo patients developed retinal breaks (1.9% versus 4.3%, respectively), also consistent with the lower rate of vitrectomy.

All AEs associated with ocriplasmin treatment were ocular events, and the majority were not Serious, mild in intensity, resolved, and therefore were not considered to be clinically significant. The only AE where a dose-response relationship was observed (based on limited data with doses other than 125 µg) was vitreous floaters. In patients who received 2 (n = 2) or 3 (n = 7) doses of ocriplasmin in the same eye, no untoward effects were observed.

Table 22. Study Eye Adverse Events Reported for at Least 2% of Patients in Phase 3, Randomized, Placebo-Controlled Studies and All Completed Studies (Safety Set)

System Organ Class Preferred Term Category	Phase 3, Randomized, Placebo-Controlled Studies		All Completed Studies	
	Placebo n=187	Ocriplasmin 125µg n=465	Control[a] n=247	Ocriplasmin Any Dose n=741
Study Eye AEs, n (%)				
Vitreous floaters	14 (7.5)	78 (16.8)	18 (7.3)	119 (16.1)
Conjunctival hemorrhage	24 (12.8)	68 (14.6)	49 (19.8)	129 (17.4)
Eye pain	11 (5.9)	61 (13.1)	19 (7.7)	90 (12.1)
Photopsia	5 (2.7)	55 (11.8)	7 (2.8)	66 (8.9)
Vision blurred	6 (3.2)	39 (8.4)	7 (2.8)	47 (6.3)
Macular hole (new or worsening)	18 (9.6)	31 (6.7)	19 (7.7)	50 (6.7)
Visual acuity reduced	8 (4.3)	29 (6.2)	8 (3.2)	41 (5.5)
Retinal edema	2 (1.1)	25 (5.4)	2 (0.8)	32 (4.3)
Visual impairment[b]	2 (1.1)	25 (5.4)	2 (0.8)	27 (3.6)
Macular edema	3 (1.6)	19 (4.1)	10 (4.0)	43 (5.8)
Intraocular pressure increased	10 (5.3)	18 (3.9)	17 (6.9)	65 (8.8)
Anterior chamber cells	5 (2.7)	17 (3.7)	12 (4.9)	57 (7.7)
Photophobia[c]	0	17 (3.7)	0	25 (3.4)
Ocular discomfort	2 (1.1)	13 (2.8)	4 (1.6)	17 (2.3)
Vitreous detachment	2 (1.1)	12 (2.6)	2 (0.8)	13 (1.8)
Iritis	0	12 (2.6)	0	12 (1.6)
Cataract	8 (4.3)	11 (2.4)	12 (4.9)	34 (4.6)
Dry eye	2 (1.1)	11 (2.4)	2 (0.8)	14 (1.9)
Conjunctival hyperemia	4 (2.1)	10 (2.2)	6 (2.4)	25 (3.4)
Metamorphopsia	1 (0.5)	10 (2.2)	1 (0.4)	14 (1.9)

Abbreviation: AEs, adverse events.
[a]Patients allocated to placebo, sham-injection, or no treatment.
[b]The verbatim term entopic phenomena (as can occur in setting of posterior vitreous detachment) was conservatively coded to the preferred term (PT) visual impairment instead of floaters/photopsia.
[c]Two reports of photosensitivity, both in TG-MV-006, that occurred in the study eye were coded to the PT photosensitivity reaction, and may represent 2 additional reports of photophobia.
Data on file, ThromboGenics.

Table 23. Suspected Adverse Drug Reactions in the Study Eye in Phase 3, Randomized, Placebo-Controlled Studies and All Completed Studies (Safety Set)

	Phase 3, Randomized, Placebo-Controlled Studies		All Completed Studies	
	Placebo n=187	Ocriplasmin 125µg n=465	Control[a] n=247	Ocriplasmin Any Dose n=741
Preferred Term	n (%)	n (%)	n (%)	n (%)
Vitreous floaters	14 (7.5)	78 (16.8)	18 (7.3)	119 (16.1)
Eye pain	11 (5.9)	61 (13.1)	19 (7.7)	90 (12.1)
Photopsia	5 (2.7)	55 (11.8)	7 (2.8)	66 (8.9)
Vision blurred	6 (3.2)	39 (8.4)	7 (2.8)	47 (6.3)
Visual acuity reduced	8 (4.3)	29 (6.2)	8 (3.2)	41 (5.5)
Visual impairment	2 (1.1)	25 (5.4)	2 (0.8)	27 (3.6)
Retinal edema	2 (1.1)	25 (5.4)	2 (0.8)	32 (4.3)
Macular edema	3 (1.6)	19 (4.1)	10 (4.0)	43 (5.8)
Anterior chamber cells	5 (2.7)	17 (3.7)	12 (4.9)	57 (7.7)
Photophobia	0	17 (3.7)	0	25 (3.4)
Ocular discomfort	2 (1.1)	13 (2.8)	4 (1.6)	17 (2.3)
Vitreous detachment	2 (1.1)	12 (2.6)	2 (0.8)	13 (1.8)
Iritis	0	12 (2.6)	0	12 (1.6)
Dry eye	2 (1.1)	11 (2.4)	2 (0.8)	14 (1.9)
Metamorphopsia	1 (0.5)	10 (2.2)	1 (0.4)	14 (1.9)
Retinal degeneration	1 (0.5)	8 (1.7)	1 (0.4)	11 (1.5)
Eyelid edema	1 (0.5)	7 (1.5)	8 (3.2)	22 (3.0)
Retinal pigment epitheliopathy	0	7 (1.5)	4 (1.6)	24 (3.2)
Macular degeneration	1 (0.5)	6 (1.3)	1 (0.4)	13 (1.8)
Miosis	0	5 (1.1)	0	5 (0.7)
Scotoma	0	5 (1.1)	0	5 (0.7)
Corneal abrasion	0	5 (1.1)	1 (0.4)	7 (0.9)
Ocular hyperemia	1 (0.5)	4 (0.9)	1 (0.4)	14 (1.9)
Conjunctival irritation	0	4 (0.9)	0	4 (0.5)

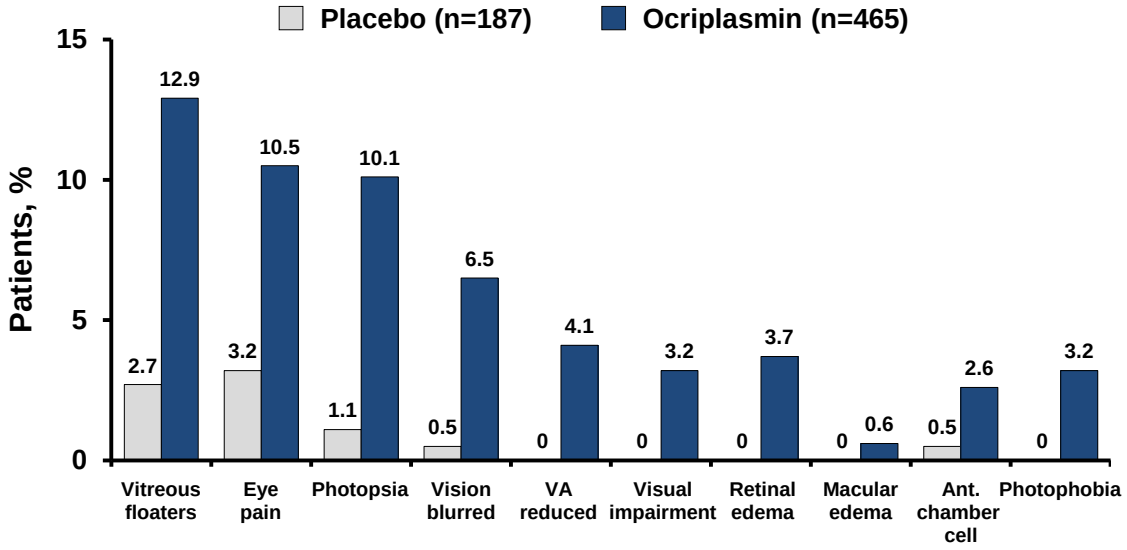
Diplopia	0	4 (0.9)	0	4 (0.5)
Visual field defect	1 (0.5)	3 (0.6)	1 (0.4)	4 (0.5)
Pupils unequal	0	3 (0.6)	0	3 (0.4)

[a]Patients allocated to placebo, sham injection, or no treatment.
Data on file, ThromboGenics.

9.4.2.1 Ocular Adverse Events by Time

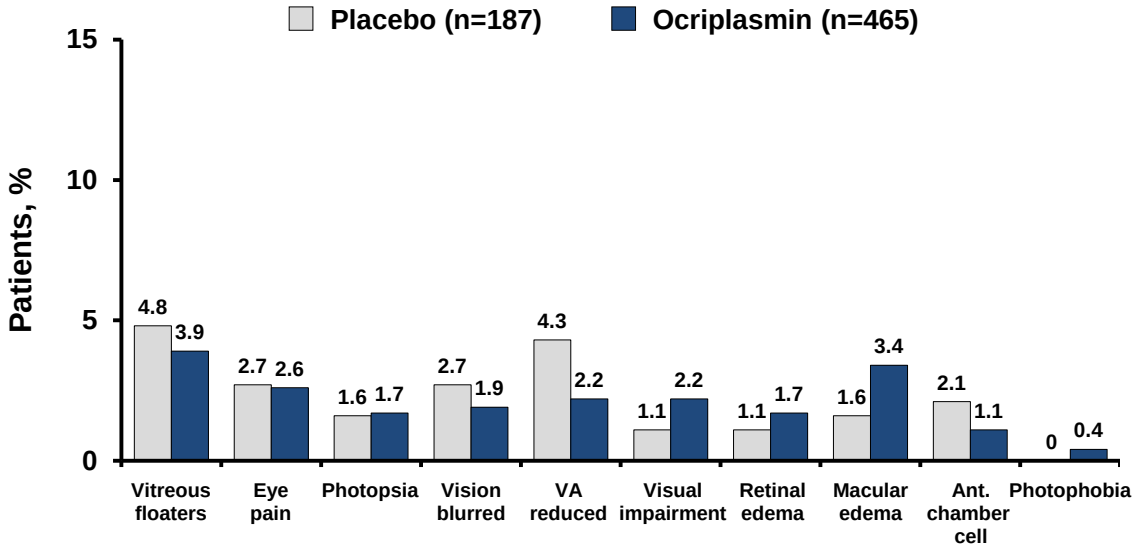
Based on the single intravitreal injection of study drug and the rapid inactivation of ocriplasmin, the incidence of suspected ADRs occurring within 7 days post-injection that were attributed as being possibly related to treatment, is considered a more reliable estimate of risk compared with events occurring later. As shown in Figures 36 and 37 for the randomized, placebo-controlled studies, the majority of the most common events occurred during the first 7 days following injection, and this is when the greatest differences between ocriplasmin and placebo were evident. The majority of these events were not Serious and mild in intensity. No relevant difference in the incidence of these events was seen between treatment groups with an onset from Day 8 to the end of the study (EOS), during which ocriplasmin patients experienced numerically lower rates of the majority of the events.

Figure 36. Post-Injection Adverse Events in the Study Eye Considered Suspected ADRs by Time to Onset in the Phase 3, Randomized, Placebo-Controlled Studies — Day 0–7 (Safety Set)



Abbreviations: ADR, adverse drug reaction; Ant., anterior; VA, visual acuity.
Data on file, ThromboGenics.

Figure 37. Post-Injection Adverse Events in the Study Eye Considered Suspected ADRs by Time to Onset in the Phase 3, Randomized, Placebo-Controlled Studies — Day 8 to End of Study (Month 6) (Safety Set)



Abbreviations: ADR, adverse drug reaction; Ant., anterior; VA, visual acuity.
Data on file, ThromboGenics.

9.4.2.2 Serious and Severe Ocular Adverse Events

Table 24 shows the Serious AEs that occurred in the randomized, placebo-controlled studies and all completed studies. By preferred term, the most commonly reported Serious AEs in the randomized, placebo-controlled studies in the ocriplasmin group were macular holes (5.2%) and vitreous adhesions (1.1%), and in the placebo group were macular holes (8.6%) and retinal detachment (1.6%). All other Serious AEs were reported in <1% of patients in both treatment groups.

In the randomized, placebo-controlled studies, 23 (4.9%) patients in the ocriplasmin group and 11 (5.9%) in the placebo group had a study eye event of severe intensity (Table 25). Among those considered possibly treatment-related, visual acuity reduced was the only preferred term reported as severe for both treatment groups (0.6% and 0.5%, respectively).

Table 24. Serious Adverse Events in the Study Eye in Phase 3, Randomized, Placebo-Controlled Studies and All Completed Studies (Safety Set)

	Phase 3, Randomized, Placebo-Controlled Studies		All Completed Studies	
	Placebo n=187	Ocriplasmin 125 µg n=465	Control[a] n=247	Ocriplasmin Any Dose n=741
Study Eye SAEs, n (%)	20 (10.7)	36 (7.7)	22 (8.9)	57 (7.7)
Preferred Term, n (%)				
Macular hole[b]	16 (8.6)	24 (5.2)	16 (6.5)	35 (4.7)
Vitreous adhesions	1 (0.5)	5 (1.1)	2 (0.8)	5 (0.7)
Visual acuity reduced	1 (0.5)	3 (0.6)	1 (0.4)	3 (0.4)
Retinal detachment	3 (1.6)	2 (0.4)	3 (1.2)	4 (0.5)
Eye inflammation	0	1 (0.2)	0	1 (0.1)
Hyphema	0	1 (0.2)	1 (0.4)	1 (0.1)
Posterior capsule opacification	0	1 (0.2)	0	2 (0.3)
Vitreous hemorrhage	0	1 (0.2)	1 (0.4)	1 (0.1)
Macular edema	1 (0.5)	0	1 (0.4)	1 (0.1)
Cataract	0	0	0	3 (0.4)
Optic disc vascular disorder	0	0	0	1 (0.1)
Retinal artery occlusion	0	0	0	1 (0.1)
Retinal vein occlusion	0	0	0	1 (0.1)
Intraocular pressure increased	0	0	0	1 (0.1)
Anterior chamber inflammation	0	0	0	1 (0.1)
Choroidal detachment	0	0	0	1 (0.1)
Macular degeneration	0	0	0	1 (0.1)
Retinal tear	0	0	0	1 (0.1)
Cataract traumatic	0	0	0	1 (0.1)
Choroidal hemorrhage	0	0	1 (0.4)	0

Abbreviation: SAE, Serious adverse event.
[a]Patients allocated to placebo, sham injection, or no treatment.
[b]New or worsening.
Data on file, ThromboGenics.

Table 25. Severe Suspected ADRs in the Study Eye in Phase 3, Randomized, Placebo-Controlled Studies and All Completed Studies (Safety Set)

Preferred Term	Phase 3, Randomized, Placebo-Controlled Studies		All Completed Studies	
	Placebo n=187	Ocriplasmin 125 µg n=465	Control[a] n=247	Ocriplasmin Any Dose n=741
Severe Study Eye Events, n (%)	11 (5.9)	23 (4.9)	13 (5.3)	33 (4.5)
Suspected ADRs, n (%)				
Visual acuity reduced	1 (0.5)	3 (0.6)	1 (0.4)	4 (0.5)
Visual impairment	0	1 (0.2)	0	1 (0.1)
Retinal edema	0	0	0	1 (0.1)
Macular edema	1 (0.5)	0	1 (0.4)	0
Photophobia	0	3 (0.6)	0	3 (0.4)
Vitreous detachment	0	1 (0.2)	0	1 (0.1)
Macular degeneration	1 (0.5)	0	1 (0.4)	0
Visual field defect	0	1 (0.2)	0	1 (0.1)

Abbreviation: ADR, adverse drug reaction.
[a]Patients allocated to placebo, sham injection, or no treatment.
Note: Preferred terms for which no suspected adverse drug reactions were reported as severe were vitreous floaters, eye pain, photopsia, vision blurred, anterior chamber cell, ocular discomfort, iritis, dry eye, metamorphopsia, retinal degeneration, eyelid edema, retinal pigment epitheliopathy, miosis, scotoma, corneal abrasion, ocular hyperemia, conjunctival irritation, diplopia, and pupils unequal.
Data on file, ThromboGenics.

9.4.3 Anatomic Retinal Findings

Anatomic retinal findings were based on AEs and the results of OCT scans. Most events were mild in severity, and, with the exception of retinal edema, the majority occurred after Day 7 post-injection. As compared with vision-related events (see Section 9.5.1), the anatomic retinal findings had longer times to resolution, and there were more unresolved events at EOS. The ongoing events occurred in both the ocriplasmin and placebo treatment groups. The most common event with a higher incidence in the ocriplasmin group versus placebo during the randomized, placebo-controlled studies and in all completed studies was retinal edema (ie, subretinal fluid/macular edema) in 9.5% versus 2.7%, and 9.7% versus 4.9%, respectively. Confounding factors, such as underlying disease and onset after vitrectomy, limit the ability to determine a causal relationship with ocriplasmin for many of these events, other than retinal edema.

9.4.3.1 Macular Holes

Consistent with the effectiveness of ocriplasmin treatment, which resulted in a 4-fold higher rate of pharmacologic macular hole closure compared with placebo, the incidence of new or worsening macular holes was lower in the ocriplasmin group than the placebo group during both the randomized, placebo-controlled studies (6.7% versus 9.6%, respectively) and in all completed studies (6.7% versus 7.7%, respectively). However, in a small subset of patients in the randomized, placebo-controlled studies, 0.6% of patients in the ocriplasmin group (3/465) and 0.5% of patients in the placebo group (1/187) who had a new or worsening macular hole within approximately 7 to 14 days post-injection also had a ≥3-line loss in BCVA at EOS.

9.4.4 AEs Known to be Associated with Intravitreal Injection Procedures

Increased IOP, intraocular inflammation, intraocular hemorrhage, and intraocular infection are known risks of an intravitreal injection procedure. Since the same injection technique and volume were used for both ocriplasmin and placebo, the incidence of these events in the placebo group serves as a basis of the procedural risk associated with the intravitreal injection procedure. A higher incidence of these types of events in the ocriplasmin group compared with control would therefore suggest a drug effect separate from a procedure-related event.

Table 26 summarizes these events for the Phase 3, randomized, placebo-controlled studies and all studies combined (infection is discussed in Section 9.4.4.1). Most events in the ocriplasmin

group began during Days 0 to 7, whereas a later onset was noted in the placebo group. Most events were mild in severity, and none were considered treatment-related.

Comparisons of the incidence of events associated with intravitreal procedures show no increased risk with ocriplasmin compared with placebo, with the exception of transient mild inflammation.

Table 26. Summary of Adverse Events Known to be Associated with Intravitreal Injection Procedures in Phase 3, Randomized, Placebo-Controlled Studies and All Completed Studies (Safety Set)

	Phase 3, Randomized, Placebo-Controlled Studies		All Completed Studies	
Preferred Term	**Placebo n=187**	**Ocriplasmin 125µg n=465**	**Controls[a] n=247**	**Ocriplasmin Any Dose n=741**
Any study eye AE, n (%)	53 (28.3)	216 (46.5)	84 (34.0)	372 (50.2)
Intraocular hemorrhage	7 (3.7)	11 (2.4)	17 (6.9)	44 (5.9)
Intraocular inflammation	7 (3.7)	33 (7.1)	18 (7.3)	90 (12.1)
IOP increase	10 (5.3)	19 (4.1)	17 (6.9)	68 (9.2)

Abbreviations: AE, adverse event; IOP, intraocular pressure.
[a]Patients allocated to placebo, sham injection, or no treatment.
Data on file, ThromboGenics.

9.4.4.1 Intraocular Infection

No cases of intraocular infections, including endophthalmitis, were reported in any patient treated with ocriplasmin.

9.4.4.2 Intraocular Pressure

The rate of clinically significant increase in IOP, defined as IOP measurement of ≥25 mm Hg and a ≥5 mm Hg increase from baseline on ocular examination, was low and comparable in both treatment groups: 7 patients (1.5%) with 10 such occurrences in the ocriplasmin group and 8 (4.3%) patients with 9 occurrences in the placebo group during the placebo-controlled studies, with no clinically meaningful between-treatment-group difference observed.

In the Phase 3, randomized, placebo-controlled studies, the mean IOP at baseline and the mean change from baseline at each visit were similar with ocriplasmin and placebo (Table 27). Patients in the ocriplasmin group experienced a slightly higher rate of IOP shifts from ≤21 mm Hg at baseline to >21 mm Hg at Day 7 than the placebo group (1.3% and 0.5%, respectively), which

was reversed by the end of the study (1.3% and 1.6%, respectively). No patient in either treatment group had an IOP >30 mm Hg at any study visit.

There was no clinically important difference in the incidence of IOP increase reported as an AE in the ocriplasmin group compared with the placebo group in the Phase 3, randomized, placebo-controlled studies (4.1% versus 5.3%), with onset during the Day 8 to EOS interval for most events. All events were of mild or moderate intensity.

Although no adverse trends in IOP elevation were observed overall, there were 3 cases of acute elevated IOP that occurred post intravitreal injection and that were considered as Serious AEs, 2 of which were reported after the data cut-off date.

Two of the events occurred in patients with exudative AMD (TG-MV-005, AMD study) and these patients had post-injection, transient, IOP-associated vision loss. In 1 patient the IOP was 44 mm Hg post-injection; the pressure returned to normal (13 mm Hg) once the eye was massaged and treated with apraclonidine. In the other patient, IOP was not measured; however, the eye was described as tense/hard to palpation. The IOP was 16 mm Hg after the eye was massaged and treated with iodipine 1%. Both patients reported transient No Light Perception (NLP)/vision loss in the injected eye. Light perception returned within 3 to 4 minutes and visual acuity returned to normal or baseline values on the same day. On Day 7, there was minimal difference in visual acuity compared with baseline values for both patients: 62 versus 66, Day 7 and baseline, respectively; and 44 to 45 versus 38, Day 7 and baseline, respectively.

The third event occurred in a patient participating in an ongoing study (TG-MV-014, Symptomatic VMA). There were 2 related events, increased IOP and non-perfusion of the optic nerve post-injection. Paracentesis was performed and the patient recovered. All of these patients are enrolled in ongoing studies and are still masked with regard to treatment received.

Acute increases in IOP including NLP are known risks of intravitreal treatment (Aiello 2004, Jager 2004, Kuppermann 2005).

Table 27. Summary of Mean Change from Baseline in Intraocular Pressure in Phase 3, Randomized, Placebo-Controlled Studies (Safety Set)

Study Visit	Phase 3, Randomized, Placebo-Controlled Studies	
	Placebo n=187	Ocriplasmin 125 µg n=465
Baseline, n	187	464
Mean (SD)	15.1 (3.25)	15.0 (2.87)
Day 7, n	183	457
Mean (SD)	14.8 (3.25)	14.5 (3.09)
Mean (SD) change from BL	-0.3 (3.14)	-0.5 (2.93)
Day 28, n	183	456
Mean (SD)	14.7 (3.45)	14.5 (3.17)
Mean (SD) change from BL	-0.4 (3.22)	-0.5 (2.89)
End of Study, n	186	464
Mean (SD)	14.6 (3.11)	14.7 (3.07)
Mean (SD) change from BL	-0.5 (3.21)	-0.2 (2.95)

Abbreviations: BL, baseline; SD, standard deviation.
Data on file, ThromboGenics.

9.4.4.3 Intraocular Inflammation

In the Phase 3, randomized, placebo-controlled studies, the overall incidence of intraocular inflammation AEs was higher in the ocriplasmin than in the placebo group (7.1% versus 3.7%). The onset was during Days 0 to 7 for most events in the ocriplasmin group and during Day 8 to the EOS in the placebo group. The incidence of drug-related AEs was 4.5% and 1.6% in the ocriplasmin and placebo groups, respectively. None of the drug-related events were considered as Serious AEs, and most were of mild intensity. The majority of events resolved spontaneously. In patients who received repeated dosing of ocriplasmin, no increase in the rate or severity of intraocular inflammation was observed. Only 1 Serious AE, anterior chamber inflammation, was reported, which occurred 1 day post-vitrectomy and resolved within 2 weeks. The investigator considered the event to be unrelated to study drug but suggested that it may have been a reaction to the triamcinolone acetonide injection administered during vitrectomy.

9.4.4.4 Intraocular Hemorrhage

In the Phase 3, randomized, placebo-controlled studies, no clinically meaningful differences between treatments were observed for the incidence of AEs in the intraocular hemorrhage category for all events (2.4% with ocriplasmin versus 3.7% with placebo) and drug-related

events (0.2% versus 1.6%, respectively). Serious AEs were reported for 2 (0.4%) patients treated with ocriplasmin and none with placebo. All events were of mild or moderate intensity, and most events in both treatment groups had onset during the Day 8 to EOS time interval and resolved in most patients. Outcome was ongoing for 0.9% and 0.5% of patients in the ocriplasmin and placebo groups, respectively.

9.4.5 Cataracts

The incidence of cataract (any event) in the Phase 3, randomized, placebo-controlled studies was 26 (5.6%) in the ocriplasmin group and 17 (9.1%) in the placebo group. In all studies combined, the incidence was 77 (10.4%) and 29 (11.7%), respectively.

The rate of cataract formation or cataract progression in the Phase 3, randomized, placebo-controlled studies was lower with placebo, 8.2% versus 11.9%, respectively (Table 28). This finding was expected, as cataract is a common complication of vitrectomy, occurring in the vast majority of phakic patients and necessitating an additional surgical procedure, cataract extraction (Benson 2001).

Table 28. Study Eye Cataract Adverse Events in Phakic Patients in Phase 3, Randomized, Placebo-Controlled Studies (Safety Set)

	Phase 3, Randomized, Placebo-Controlled Studies	
Preferred Term	**Placebo n=134**	**Ocriplasmin 125µg n=293**
Any lens opacity-related event, n (%)	16 (11.9)	24 (8.2)
Cataract	8 (6.0)	11 (3.8)
Cataract cortical	3 (2.2)	3 (1.0)
Cataract nuclear	3 (2.2)	5 (1.7)
Cataract subcapsular	1 (0.7)	4 (1.4)
Posterior capsule opacification	2 (1.5)	2 (0.7)

Data on file, ThromboGenics.

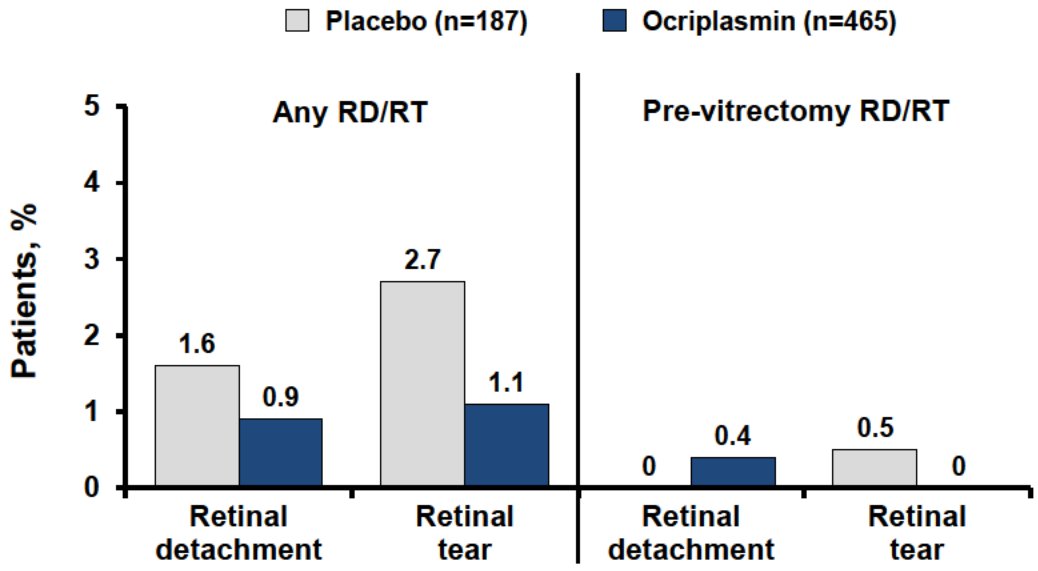
9.4.6 Retinal Breaks

Retinal breaks, including tears and detachment, have been associated with naturally occurring PVD and with surgically induced PVD (Guillaubey 2007, Ramkissoon 2010, Rizzo 2010), and so are theoretical risks with pharmacologic vitreolysis. In the Phase 3, randomized, placebo-controlled studies, the rate of retinal breaks post-injection was low in both treatment groups and was lower for those receiving ocriplasmin: 1.9% and 4.3% with ocriplasmin and placebo

treatment, respectively (Figure 38). Most events occurred during or after vitrectomy and were considered non-drug-related. The investigator considered retinal detachment to be a Serious AE for 2 (0.4%) ocriplasmin-treated and 3 (1.6%) placebo-treated patients. All retinal tears were considered not Serious.

The rate of retinal breaks in all completed studies also was low and was similar between the ocriplasmin and control groups. As more placebo than ocriplasmin patients had vitrectomy surgery, the higher incidence of retinal breaks in the placebo group may reflect the vitrectomy-associated risk of this event.

Figure 38. Proportion of Patients with Retinal Tear or Detachment in Phase 3, Randomized, Placebo-Controlled Studies (Safety Set)



Abbreviations: RD, retinal detachment; RT, retinal tear.
Data on file, ThromboGenics.

9.5 AEs of Special Interest

The AEs of special interest occurred at low rates and included acute visual function changes (acute decrease in vision, dyschromatopsia, and ERG changes) and lens instability/subluxation.

9.5.1 Acute Visual Function Changes

9.5.1.1 Acute Decrease in Vision

A total of 9 ocriplasmin-treated patients from the completed and ongoing studies had temporary, post-injection Serious or severe AEs related to acute vision decrease within 24 hours of injection. Three of these patients were enrolled in the Phase 3, placebo-controlled studies and 6 in other studies (Table 29). In all but 1 case, the acute vision decrease resolved; the lack of resolution in the remaining case was attributed to the patient's concurrent retinal disease (macula-off retinal detachment and exudative AMD). The median time to full recovery of visual acuity was approximately 2 weeks; the longest was 1 year in a patient who required cataract surgery unrelated to study treatment. Rapid VMA resolution was observed on OCT in 8 of the 9 cases. In 1 patient, VMA status is unknown.

Table 29. Temporary Acute Decrease in Vision in Patients Treated with Ocriplasmin: Phase 3, Randomized, Placebo-Controlled Studies and Other Studies

	Baseline VA, Snellen	VA Change	VA at Last Follow-up
Phase 3, Randomized, Placebo-Controlled Studies	20/25	20/200	20/20
	20/80	Hand motion	20/60
	20/50	20/200	20/32
Other Studies	20/100	Hand motion	20/100
	20/80	Hand motion	20/320[a]
	20/80	Count fingers	20/80
	20/40	20/200	20/50
	20/32	20/200	20/40
	20/32	20/150	20/40

Abbreviation: VA, visual acuity.
[a]Lack of visual acuity recovery attributed to macula-off retinal detachment and underlying exudative AMD.
Data on file, ThromboGenics.

9.5.1.2 Dyschromatopsia

Dyschromatopsia was reported in 17 patients (1.7%) treated with ocriplasmin (described as yellow-tinted vision) and none with placebo. The majority of cases were reported from 2 uncontrolled, open-label clinical studies conducted in the same center. The majority of cases

were rated as not Serious and mild, except for 1 case that was considered Serious and of severe intensity. While not an expected AE, the majority of dyschromatopsia cases were mild. All but 2 cases resolved; 1 patient had underlying disease (adult onset vitelliform macular dystrophy) and 1 patient who is currently being followed. Two patients were lost to follow-up, and the remaining 13 of 17 cases resolved within a median time of 3 months.

9.5.1.3 ERG Changes

ERG changes were reported in 11 of 141 (7.8%) ocriplasmin-treated patients who had ERG evaluations. These were described as a- and b-wave amplitude decreases occurring during the first month after injection. Nine of these patients also had dyschromatopsia. As in the dyschromatopsia cases summarized above, the majority of cases were reported from the same 2 uncontrolled, open-label clinical studies conducted in the same center. In 6 of the 11 cases, the ERG changes resolved (median time, 6 months); 3 patients did not have follow-up ERGs, and 1 patient is being followed. The 1 case that did not resolve is the patient described above with concurrent vitelliform macular dystrophy. This existing condition was thought to be a factor for the lack of resolution.

Visual acuity in all patients returned to baseline values with the exception of the 1 patient with the underlying condition of vitelliform dystrophy.

9.5.1.4 CRC Assessment of Dyschromatopsia/ERG Changes

Three masked assessors from an independent CRC reviewed the OCT scans from patients with Serious/severe acute visual impairment and from the randomized, placebo-controlled studies and 2 open-label studies. The reviewers concluded that the acute vision decrease, dyschromatopsia, and/or ERG findings appeared to be due to a disruption of the retina at the photoreceptor level with subsequent evidence of recovery.

The reversibility of the notable events of acute vision decrease, dyschromatopsia, and ERG changes at EOS are consistent with the OCT findings of photoreceptor recovery.

9.5.2 Lens Safety

One case of drug-related lens subluxation and 1 case of lens instability where drug causality could not be ruled out were reported. Subluxation of the lens occurred in a 4-month old, extremely low-birth-weight premature male infant with significant ongoing medical and ocular

conditions enrolled in a Phase 2, randomized, placebo-controlled study of ocriplasmin 175 µg in infants and children scheduled for vitrectomy (TG-MV-009). The neonate received a single intravitreal injection of ocriplasmin 175 µg in the left eye approximately 1 hour before vitrectomy for retinopathy of prematurity. The investigator reported that approximately half of the 100 µL volume of injection refluxed out, and postulated that study medication may have had local access to the zonules, due to injection difficulties that resulted in subsequent dehiscence. The smaller eye volume of the premature infant, the larger ocriplasmin dose, and the possible access of study drug to the zonules were all considered by the Sponsor as potential factors in the development of this event. The infant received the same ocriplasmin dose in the fellow eye 1 week later and lens subluxation did not occur. None of the other 15 pediatric eyes treated with ocriplasmin during clinical development had this finding, nor has any adult ocriplasmin-treated patient.

A case of lens instability was observed in an adult during a vitrectomy that occurred 323 days following injection of 125 µg ocriplasmin in the TG-MV-007 study; no clinical signs were noted prior to the vitrectomy. This event was moderate in severity and the investigator considered it possibly related to ocriplasmin treatment. Causality with ocriplasmin cannot be assigned with certainty in this case due to the length of time after ocriplasmin administration, the lack of clinical signs, and the occurrence during vitrectomy.

No other case of phacodonesis (ie, tremulousness of the lens) was reported as an AE or observed during ocular examinations. Based on the proteolytic activity of ocriplasmin, the potential for subluxation of the lens cannot be ruled out, but the risk in adults is considered low.

9.6 Immunogenicity Risk

Ocriplasmin has 100% homology to the amino acid sequence of human plasmin/plasminogen. It is also highly similar to the human protein at the level of the secondary and tertiary structure (Parry 1998, Esmon 1998). Due to its structure, low molecular weight, and solubility, as well as the route, dose, and frequency of administration (ie, single intravitreal dose of 125 µg), the risk of a clinically significant immune response is considered low. This is supported by the findings from the intravitreal clinical program as well as clinical vascular studies in which no drug-related

hypersensitivity reactions, including uveitis or anaphylaxis, were observed. Based on the totality of these findings, the immunogenicity risk of ocriplasmin is considered to be low.

9.7 Safety Conclusions

Ocriplasmin has an acceptable safety profile for the treatment of symptomatic VMA including macular hole and was well tolerated in studies with follow-up extending to 1 year. All AEs associated with ocriplasmin treatment were ocular, which is consistent with the route of administration, rapid inactivation, and limited systemic bioavailability of the drug. Most of the AEs occurred within the first 7 days following injection. The most common AEs were consistent with pharmacologic vitreolysis (eg, vitreous floaters or photopsia) or were related to the procedure itself (eg, intraocular inflammation and irritation). The majority of events were not Serious, mild in intensity, and resolved quickly. The most notable safety findings were related to visual function changes (acute vision decrease, dyschromatopsia, and ERG changes). Most of these events were mild to moderate in nature and resolved within 2 weeks. No safety signals emerged during the clinical development program for retinal breaks, cataracts, intraocular hemorrhage, intraocular infection, or increased IOP. The risk of lens subluxation is considered to be low.

Importantly, ocriplasmin treatment led to resolution of the underlying condition; thus, the drug was associated with lower rates of VMA progression-related sequelae (eg, macular hole) and vitrectomy-related complications (eg, retinal breaks or cataracts).

10 BENEFIT-RISK

Ocriplasmin has a positive benefit-risk profile for the treatment of symptomatic VMA. In ocriplasmin-treated patients who achieve VMA resolution or full thickness macular hole closure at Day 28, there is a meaningful benefit in terms of vision and visual function. In addition, resolution of the underlying condition will halt disease progression and reduce the associated disease burden. Furthermore, patients with VMA resolution or macular hole closure are less likely to require vitrectomy and experience the subsequent complications resulting from surgery, which is associated with a long recovery time to functional vision, the need for a second surgery (ie, cataract), and the post-operative burden on both patients and caregivers.

In those patients who do not achieve VMA resolution or macular hole closure, the risks of ocriplasmin therapy are low. The majority of adverse events are mild or moderate and transient. Patients who do not respond to ocriplasmin therapy still have the option of vitrectomy without any adverse impact on the outcome.

Ocriplasmin therapy administered as a single intravitreal injection provides an office-based treatment option. This less invasive procedure provides the first alternative to surgery and thus allows for an early intervention.

10.1 Benefits of Ocriplasmin for the Proposed Indication

The efficacy of ocriplasmin for the treatment of symptomatic VMA including macular hole has been demonstrated in 2 Phase 3, randomized, placebo-controlled studies.

Both studies showed a statistically significant difference in favor of ocriplasmin for achieving the primary efficacy endpoint, OCT-confirmed resolution of VMA at Day 28 as assessed by a masked CRC. Ocriplasmin had a rapid onset of action, with results seen as early as 7 days after injection and sustained throughout the 6-month studies. In patients with a FTMH at baseline, 40.6% of those treated with ocriplasmin achieved pharmacologic macular hole closure, an outcome that only rarely occurs without treatment (Ezra 2001, Kim 1996). The ability to treat the underlying condition pharmacologically also led to fewer ocriplasmin-treated patients requiring vitrectomy, compared with placebo. Ocriplasmin treatment led to more patients gaining ≥2 or ≥3 lines of BCVA at Month 6, and to improvements in vision-related quality of life assessments (VFQ-25).

Ocriplasmin treatment offers other potential benefits compared with current approaches. For many patients observed over time (ie, watchful waiting), the disease progresses such that vitrectomy may become unavoidable. However, the functional benefit of vitrectomy may be diminished by irretrievable vision loss. Earlier surgical intervention has been shown to improve visual outcomes (Melberg 1995, Sonmez 2008); earlier pharmacologic intervention may provide similar benefits, while avoiding vitrectomy-associated risks (eg, retinal tears and detachments) and the need for a second surgery for cataract. Ocriplasmin has the potential for earlier intervention through use of an office-based intravitreal injection. Compared with vitrectomy, ocriplasmin therapy requires a relatively uncomplicated post-treatment period for patients and

their families. Intravitreal injection results in less pain and discomfort, no extended periods of face-down immobilization, less time off from work, a shorter recovery period, and fewer follow-up clinic visits than vitrectomy. Overall, this therapy results in a considerably lower treatment burden.

10.2 Risks of Ocriplasmin

Ocriplasmin is well tolerated, and the drug effects are localized to the eye, as would be expected with an intravitreal drug that is rapidly inactivated and has limited systemic exposure. The most common AEs associated with ocriplasmin were consistent with the vitreolytic activity of the drug (eg, vitreous floaters and photopsia, which are common symptoms of PVD) or were associated with the injection procedure (eg, intraocular inflammation and irritation).

The principle safety findings were related to changes in vision function, which were usually mild-to-moderate in severity. Approximately 1% of patients experienced Serious or severe acute vision decreases following the intravitreal injection. The decreases were transient and resolved in all but 1 patient. In the setting of vitrectomy, short-term but significant post-surgical vision loss is expected, and for this reason visual acuity is typically not measured until 7 to 10 days post-vitrectomy.

Dyschromatopsia and ERG changes occurred in a small percentage of patients, the majority of which resolved. Lens findings were uncommon, and based on the mechanism of action of ocriplasmin, a causal relationship cannot be ruled out; however, the risk in adults appears to be low.

Other potential risks associated with ocriplasmin intravitreal injection include intraocular infection, hemorrhage, and increased IOP. No case of endophthalmitis was reported in patients treated with ocriplasmin; nevertheless, the potential for intraocular infection must be considered a risk with any product administered via intravitreal injection. The use of standard precautions as recommended in the product labeling and established guidelines should prevent or limit intravitreal injection-related risks.

A potential risk of ocriplasmin treatment is the exposure to an unnecessary intravitreal injection in patients whose symptomatic VMA would have resolved spontaneously. However, the rate of spontaneous vitreoretinal separation is low (Hikichi 1995), as are the risks of ocriplasmin

intravitreal injection. An additional potential risk is the possible delay of a surgical procedure in a patient who receives the injection and does not respond. In clinical practice, not all patients will respond to a given therapy. However, ocriplasmin treatment allows for earlier intervention and the ability to determine the response to treatment within 28 days, a relatively short period of time for most patients with symptomatic VMA.

10.3 Benefit/Risk Conclusion

Ocriplasmin has a favorable benefit/risk profile for the treatment of symptomatic VMA including macular hole. At present, no pharmacologic treatment options are available for patients with symptomatic VMA. The current standard of care is watchful waiting, often followed by vitrectomy. During the watchful-waiting period, the patients' symptoms are untreated, exposing the individuals to risks of disease progression, complications, and in some cases, significant irreversible vision loss. Although highly effective, vitrectomy is a major surgical procedure that carries potential sight-threatening risks and a substantial post-treatment burden for patients and their families. As a consequence, new treatment options are needed.

Ocriplasmin, which is designed to liquefy the vitreous and cleave the bonds causing vitreomacular adhesion, would allow ophthalmologists to provide an alternative therapy to patients with symptomatic VMA earlier in the course of disease, before considerable visual function is lost and complications develop. Patients would not have to undergo a prolonged and stressful period of watchful waiting. Ocriplasmin intravitreal injection represents a major advance in the care of patients with symptomatic VMA.

11 CONCLUSION

Ocriplasmin is the first pharmacologic treatment for symptomatic VMA including macular hole. When successful, the anatomic result of treatment is the same as that achieved with vitrectomy. The efficacy of ocriplasmin has been demonstrated in 2 randomized, placebo-controlled studies. Patients treated with a single intravitreal injection of ocriplasmin were significantly more likely to have VMA resolution, closure of macular hole, and were less likely to undergo vitrectomy. Ocriplasmin-treated patients had clinically meaningful improvements in vision. Patients not achieving VMA resolution with ocriplasmin can still be offered vitrectomy, and surgical outcomes have not been compromised in these cases.

No systemic risks of ocriplasmin intravitreal injection are expected, and none has been identified in the clinical studies to date. Most of the AEs were consistent with the vitreolytic activity of ocriplasmin or route of administration and were mild-to-moderate in severity. The majority resolved in a short period of time.

Ocriplasmin also offers the opportunity to treat patients earlier after initial presentation, potentially leading to preservation of visual acuity and better overall long-term outcomes.

The available evidence supports a positive benefit-risk balance. Ocriplasmin has the potential to improve the treatment of symptomatic VMA including macular hole by offering ophthalmologists and their patients a pharmacologic treatment option for this progressive and potentially sight-threatening condition.

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APPENDICES

APPENDIX A: Glossary of Selected Terms

Term	Definition
Dyschromatopsia	General term given to deficiencies of color vision, especially acquired defects.
Early **T**reatment **D**iabetic **R**etinopathy **S**tudy visual acuity chart (ETDRS)	The ETDRS chart to test visual acuity was developed for use in the ETDRS study in patients with diabetic retinopathy (Ferris 1982; Ferris 1987), and has become the standard for acuity testing in clinical registration studies. Each line of the chart has 5 letters, and the individual rows are balanced for letter difficulty. Spacing is standardized: the space between each letter is the width of one letter, and there is a logarithmic progression of letter size down the rows (see sample below, which is not to scale). Mean visual acuity and mean change in visual acuity can also be calculated from the patients' responses. 
Electroretinogram (ERG)	Recording of mass electrical response of the retina when it is stimulated by light. It is recorded by placing an electrode in contact with the cornea (often with the aid of a contact lens) or around the eye under the eyelid. A second electrode is placed either on the forehead or the face. The response is complex as many cells of various types contribute to it and varies according to whether the eye is dark or light adapted, the color of the stimulus, the health of the retina, etc. The curve consists of 2 major components: a negative a-wave and a positive b-wave. The a-wave originates in the photoreceptors and the b-wave originates in the bipolar and Mueller cells. Both waves also have a photopic and a scotopic component.
Epiretinal membrane (ERM)	A pathologic membrane partially covering the surface of the retina, probably originating chiefly from the retinal pigment epithelial and glial cells.
Inner limiting membrane (ILM)	The boundary between the retina and the vitreous body, formed by astrocytes and the end feet of Mueller cells. It is separated from the vitreous humor by a basal lamina.

Term	Definition
Macular hole	A condition in which there is a partial or full thickness absence of the retina in the macular area. It appears ophthalmoscopically as a round or oval, well defined, reddish spot at the macula. There is metamorphopsia, loss of visual acuity, and a central scotoma.
Metamorphopsia	An anomaly of visual perception in which objects appear distorted in shape or of different size or in a different location than the actual object.
Phacodonesis	Tremulousness condition of the crystalline lens.
Photopsia	The sensation of seeing lights, sparks, or colors, caused by retinal or cerebral disease.
Subluxation of the lens	Luxation of the lens is pathological and complete dislocation of the lens relative to the pupil. If the luxation is incomplete it is called subluxation of the lens (or dislocation or ectopia lentis).
Vitreous floaters	Heterogeneities in the vitreous humor which may be of embryonic origin or pathological (eg, in posterior vitreous detachment, retinal detachment). The patient sees spots which float as the eye moves.

APPENDIX B: THE NATIONAL EYE INSTITUTE 25-ITEM VISUAL FUNCTIONING QUESTIONNAIRE

The National Eye Institute (NEI) sponsored the development of the 25-Item Visual Functioning Questionnaire (VFQ-25) with the goal of creating a survey tool that would measure the dimensions of self-reported vision targeted health status that are most important for persons who have chronic eye disease. The survey measures the influence of visual disability and visual symptoms on generic health domains such as emotional well-being and social functioning, in addition to task-oriented domains related to daily visual functioning. Questions included in the VFQ-25 represent the content identified during a series of condition-specific focus groups with subjects who had age-related cataracts, glaucoma, age-related macular degeneration, diabetic retinopathy, or cytomegalovirus retinitis.

The VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. The VFQ-25 takes approximately 15 minutes to administer. Improvement in the VFQ-25 was evaluated using individual scores, subscale scores, and the global composite score.

Patients in TG-MV-006 and TG-MV-007 were asked to complete this self-administered survey at baseline and 6 months after baseline.

National Eye Institute
Visual Functioning Questionnaire - 25 (VFQ-25)

version 2000

(SELF-ADMINISTERED FORMAT)

January 2000

The following is a survey with statements about problems which involve your vision or feelings that you have about your vision condition. After each question please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses, please answer all of the following questions as though you were wearing them.

INSTRUCTIONS:

1. In general we would like to have people try to complete these forms on their own. If you find that you need assistance, please feel free to ask the project staff and they will assist you.

2. Please answer every question (unless you are asked to skip questions because they don't apply to you).

3. Answer the questions by circling the appropriate number.

4. If you are unsure of how to answer a question, please give the best answer you can and make a comment in the left margin.

5. Please complete the questionnaire before leaving the center and give it to a member of the project staff. Do not take it home.

6. If you have any questions, please feel free to ask a member of the project staff, and they will be glad to help you.

STATEMENT OF CONFIDENTIALITY:

All information that would permit identification of any person who completed this questionnaire will be regarded as strictly confidential. Such information will be used only for the purposes of this study and will not be disclosed or released for any other purposes without prior consent, except as required by law.

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is:
(Circle One)

Excellent 1
Very Good 2
Good 3
Fair 4
Poor 5

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?
(Circle One)

Excellent 1
Good 2
Fair 3
Poor 4
Very Poor 5
Completely Blind 6

3. How much of the time do you worry about your eyesight?
(Circle One)

None of the time..... 1
A little of the time..... 2
Some of the time..... 3
Most of the time 4
All of the time?..... 5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

None 1
Mild..... 2
Moderate 3
Severe, or..... 4
Very severe?..... 5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:
(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this ..... ….6

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:
(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?
(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

8. How much difficulty do you have reading street signs or the names of stores?
(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?
(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?
(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?
(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?
(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants
(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?
(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

15. Are you currently driving, at least once in a while?
(Circle One)

Yes ..... 1 *Skip To Q 15c*

No 2

15a. IF NO: Have you never driven a car or have you given up driving?
(Circle One)

Never drove ..... 1 *Skip To Part 3, Q 17*

Gave up..... 2

15b. IF YOU GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?
(Circle One)

Mainly eyesight ..... 1 *Skip To Part 3, Q 17*

Mainly other reasons ..... 2 *Skip To Part 3, Q 17*

Both eyesight and other reasons ... 3 *Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:
(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4

16. How much difficulty do you have <u>driving at night</u>? Would you say you have:
(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Have you stopped doing this because of your eyesight..... 5
Have you stopped doing this for other reasons or are you not interested in doing this 6

16A. How much difficulty do you have <u>driving in difficult conditions, such</u> <u>as in bad weather, during rush hour, on the freeway, or in city traffic</u>? Would you say you have:
(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Have you stopped doing this because of your eyesight..... 5
Have you stopped doing this for other reasons or are you not interested in doing this 6

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, please circle the number to indicate whether for you the statement is true for you <u>all</u>, <u>most</u>, <u>some</u>, <u>a little</u>, or <u>none</u> of the time.

(Circle One On Each Line)

READ CATEGORIES:	**All of the time**	**Most of the time**	**Some of the time**	**A little of the time**	**None of the time**
17. <u>Do you accomplish less</u> than you would like because of your vision?	**1**	**2**	**3**	**4**	**5**
18. <u>Are you limited</u> in how long you can work or do other activities because of your vision?	**1**	**2**	**3**	**4**	**5**
19. How much does pain or discomfort <u>in or around</u> <u>your eyes</u>, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	**1**	**2**	**3**	**4**	**5**

For each of the following statements, please circle the number to indicate whether for you the statement is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.
(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.....	**1**	**2**	**3**	**4**	**5**
21. I feel frustrated a lot of the time because of my eyesight.....	**1**	**2**	**3**	**4**	**5**
22. I have much less control over what I do, because of my eyesight.	**1**	**2**	**3**	**4**	**5**
23. Because of my eyesight, I have to rely too much on what other people tell me..	**1**	**2**	**3**	**4**	**5**
24. I need a lot of help from others because of my eyesight.....	**1**	**2**	**3**	**4**	**5**
25. I worry about doing things that will embarrass myself or others, because of my eyesight.....	**1**	**2**	**3**	**4**	**5**

Appendix of Optional Additional Questions

SUBSCALE: GENERAL HEALTH

A1. How would you rate your <u>overall health</u>, on a scale where zero is <u>as bad as death</u> and 10 is <u>best</u> possible health?
(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										**Best**

SUBSCALE: GENERAL VISION

A2. How would you rate your eyesight now (with glasses or contact lens on, if you wear them), on a scale of from 0 to 10, where zero means the worst possible eyesight, as bad or worse than being blind, and 10 means the best possible eyesight?
(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										**Best**

SUBSCALE: NEAR VISION

A3. Wearing glasses, how much difficulty do you have <u>reading the small print in a telephone book, on a medicine bottle, or on legal forms</u>? Would you say:
(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this..... 6

A4. Because of your eyesight, how much difficulty do you have figuring out whether bills you receive are accurate?

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

A5. Because of your eyesight, how much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

SUBSCALE: DISTANCE VISION

A6. Because of your eyesight, how much difficulty do you have recognizing people you know from across a room?

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not

interested in doing this 6

A7. Because of your eyesight, how much difficulty do you have taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking)?
(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

A8. Because of your eyesight, how much difficulty do you have seeing and enjoying programs on TV?
(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

SUBSCALE: SOCIAL FUNCTION

A9. Because of your eyesight, how much difficulty do you have entertaining friends and family in your home?
(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4

Stopped doing this because of your eyesight 5

Stopped doing this for other reasons or not interested in doing this 6

SUBSCALE: DRIVING

A10. [This item, "driving in difficult conditions", has been included as part of the base set of 25 items as item 16a.]

SUBSCALE: ROLE LIMITATIONS

A11. The next questions are about things you may do because of your vision. For each item, please circle the number to indicate whether for you this is true for you all, most, some, a little, or none of the time.
(Circle One On Each Line)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Do you have more help from others because of your vision?	**1**	**2**	**3**	**4**	**5**
b. Are you limited in the kinds of things you can do because of your vision?	**1**	**2**	**3**	**4**	**5**

SUBSCALES: WELL-BEING/DISTRESS (#A12) and DEPENDENCY (#A13)

The next questions are about how you deal with your vision. For each statement, please circle the number to indicate whether for you it is definitely true, mostly true, mostly false, or definitely false for you or you don't know.
(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
A12. I am often irritable because of my eyesight.	**1**	**2**	**3**	**4**	**5**
A13. I don't go out of my home alone, because of my eyesight.....	**1**	**2**	**3**	**4**	**5**

APPENDIX C: Deaths in the Ocriplasmin Clinical Program

A total of 8 deaths occurred during the clinical development program: 6 of 741 (0.8%) ocriplasmin-treated patients and 2 of 247 (0.8%) control patients. The 2 control patients had received sham injections. One ocriplasmin-treated patient had received the 75 µg dose and 5 had received 125 µg. Each patient died of a non-ocular AE that was determined to be unrelated to the study drug.

Patient / Study	Treatment / Date of Injection	Event as Reported / MedDRA Preferred Term	Narrative
74-year-old male Phase 2 TG-MV-002	Sham / 10-Dec-2008	Cardiac arrest	Subject experienced a fatal cardiac arrest (b) (6) days after study drug single administration. Medical history of diabetes mellitus, hypercholesterolemia and cardiomyopathy. Concomitant medications relevant to SAE were insulin; molsidomine; acetylsalicylic acid; perindopril; metoprolol; moxonidine; ezetimibe; amitriptyline; tetrazepam; levocetirizine.
82-year-old male Phase 2 TG-MV-002	Sham / 30-Mar-2007	Intestinal obstruction	On 07-April-2007, 8 days post study drug injection, subject experienced an intestinal obstruction. On (b) (6) resection of small bowel and on (b) (6) an evisceration of the small bowel. Patient died 2 days later on (b) (6). Medical history of insulin-dependent diabetes mellitus, Parkinson's, left ventricular hypertrophy and anemia. Subject was on a number of concomitant medications relevant to SAE.

Patient / Study	Treatment / Date of Injection	Event as Reported / MedDRA Preferred Term	Narrative
75-year-old male Phase 2 TG-MV-003	Ocriplasmin 75 µg / 21-Mar-2008	Myocardial infarction	On [redacted] (b) (6) months after ocriplasmin injection, the patient had a myocardial infarction and was pronounced dead at home. He had no relevant medical history to this event; his history included localized arthritis, skin cancer, and enlarged prostate. Concomitant medications included finasteride, tamsulosin hydrochloride, multivitamins, ibuprofen, glucosamine, fluorescein sodium, tropicamide, phenylephrine, proparacaine, prednisolone acetate, and cyclopentolate. No autopsy. The investigator considered the SAE to be unrelated to study drug.
81-year-old female Phase 3, randomized, placebo-controlled study TG-MV-006	Ocriplasmin 125 µg / 22-Apr-2009	Cerebral hemorrhage	Patient received ocriplasmin 125 µg intravitreal injection on 22-April-2009. On 18-June-2009, she underwent vitrectomy, membrane peeling, and 20% SF6 injection because vitreomacular traction/pseudohole did not improve from baseline. At her first post-operative (Day [redacted] (b) (6)) visit on [redacted] (b) (6) she did not voice complaints and said she was thrilled with the post-operative results. Later that day while shopping, she tripped and fell, lost consciousness, and never regained it. CT scans taken at local trauma center revealed severe brain hemorrhage. Relevant medical history included coronary artery disease; myocardial infarct; high blood pressure; osteoporosis; type 2 diabetes mellitus. Concomitant medications at the time of the event included aspirin and clopidogrel bisulfate.
84-year-old female Phase 3, randomized, placebo-controlled study TG-MV-006	Ocriplasmin 125 µg / 08-May-2009	Lung neoplasm malignant	On [redacted] (b) (6), subject was hospitalized for a scan of the pancreas and a series of biopsies of the lung, pancreas, and lumps on her head. Diagnosed with lung cancer on 20-Aug-2009 and died [redacted] (b) (6) days later. Relevant medical history of bilateral breast biopsies (1990s—no results reported); hypertension, hypercholesterolemia; and gastroesophageal reflux disease. Subject was a nonsmoker and had no family history of cancer. No concomitant medications reported.

Patient / Study	Treatment / Date of Injection	Event as Reported / MedDRA Preferred Term	Narrative
83-year-old female Phase 3, randomized, placebo-controlled study TG-MV-006	Ocriplasmin 125 µg / 22-Jul-2009	Cardiac failure congestive	(b) (6) months post study drug single injection, subject experienced worsening of her underlying congestive heart failure and died at home on (b) (6) No autopsy performed; no death certificate available. Relevant medical history included chronic obstructive pulmonary disease; emphysema; hypertension; vertigo; congestive heart failure; myocardial infarction; gastroesophageal reflux disorder. Concomitant medications relevant to the SAE included aspirin and nitroglycerin; metoprolol tartrate; ramipril; furosemide and verapamil; albuterol and tiotropium.
76-year-old female Phase 3, randomized, placebo-controlled study TG-MV-007	Ocriplasmin 125 µg / 16-Sep-2009	Brain cancer metastatic	On (b) (6), subject was hospitalized and diagnosed with terminal brain cancer. Treated with dexamethasone and discharged on (b) (6) Patient died at home on (b) (6). Relevant medical history included vaginal cancer and lung cancer. No concomitant medications reported as relevant to the SAE.
88-year-old female Phase 3, randomized, placebo-controlled study TG-MV-007	Ocriplasmin 125 µg / 11-Jun-2009	Lung neoplasm, malignant	Subject experienced worsening of underlying metastatic lung cancer and died at home on (b) (6). No autopsy was performed. Relevant medical history included colon cancer and lung cancer. Concomitant treatments relevant to the SAE included oxygen, morphine, and alprazolam.

Abbreviations: CT, computed tomography; SAE, Serious adverse event.
Data on file, ThromboGenics.